

Appendix A. Search Strategy

Resources Searched

ECRI Institute information specialists searched the following databases for relevant information. Search terms and strategies for the bibliographic databases appear below.

Bibliographic Databases Searched

Name	Date Limits	Platform/Provider
The Cochrane Central Register of Controlled Trials (CENTRAL)	1994 through July 11, 2014	Wiley
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	1994 through July 11, 2014	Wiley
Database of Abstracts of Reviews of Effects (DARE)	1994 through July 11, 2014	Wiley
EMBASE (Excerpta Medica)	1994 through June 2014	Embase.com
Health Technology Assessment Database (HTA)	1994 through June 2014	Wiley
MEDLINE	1994 through June 2014	Embase.com
PubMed (In-process and Publisher records)	1994 through June 2014	NLM
U.K. National Health Service Economic Evaluation Database (NHS EED)	1994 through June 2014	Wiley

Gray Literature Resources Searched

Name	Date Limits	Platform/Provider
American Society of Transplantation (AST)	searched July 24, 2014*	AST
American Society of Transplant Surgeons (ASTS)	searched July 24, 2014*	ASTS
American Transplant Congress	2013 and 2014 meeting abstracts	ASTS
Clinical Trials.gov	1994 through July 15, 2014	U.S. National Institutes of Health (NIH)
Centre for Evidence in Transplantation (CET)	Website searched July 24, 2014* Trial Watch database searched January 1, 2013 through July 24, 2014	CET
Centers for Disease Control and Prevention (CDC)	searched July 24, 2014*	CDC
Centers for Medicare and Medicaid	1994 through July 15, 2014	CMS
Health Devices	1994 through July 15, 2014	ECRI Institute
Health Technology Assessment Information Service (HTAIS) website	1994 through July 15, 2014	ECRI Institute
Healthcare Product Comparison Systems (HPCS) website	1994 through July 20, 2014	ECRI Institute
Healthcare Standards database	1994 through July 15, 2014	ECRI Institute
Infectious Diseases Society of America (IDSA)	1994 through September 9, 2014	IDSA (searched via Google search engine)
MedlinePlus	searched July 24, 2014	National Library of Medicine (NLM)
Medscape	2009 through July 23, 2014	WebMD
National Guideline Clearinghouse™ (NGC)	searched July 14, 2014*	Agency for Healthcare Research and Quality (AHRQ)

Gray Literature Resources Searched (continued)

Name	Date Limits	Platform/Provider
National Institute of Health and Clinical Excellence (NICE)	searched July 25, 2014*	National Health Service (UK)
National Kidney Foundation (NKF)	Searched July 24, 2014*	NKF
Organ Procurement and Transplantation Network (OPTN)	searched Aug 12, 2014*	Health Resources and Services Administration (HRSA)
Scientific Registry of Transplant Recipients	searched Aug 12, 2014*	Health Resources and Services Administration (HRSA)
U.S. Food and Drug Administration (FDA)	searched July 14, 2014*	FDA
World Transplant Congress (WTC)	2014 meeting abstracts	WTC

*Search date limits were not applied.

Hand Searches of Journal and Gray Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

Topic-specific Search Terms

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

Controlled Vocabulary and Keywords

Concept	Controlled Vocabulary	Keywords
Calcineurin Inhibitors	EMBASE (EMTREE) 'advagraf'/exp 'astagraf'/exp 'calcineurin inhibitor'/exp 'ciclosporine'/exp 'cipol'/exp 'cyclokat'/exp 'cyclosporin'/exp 'deximune'/exp 'gengraf'/exp 'hecoria'/exp 'immunosporin'/exp 'implanta'/exp 'mustopic oint'/exp 'neoral'/exp 'prograf'/exp 'tacrolimus'/exp 'tsukubaenolide'/exp	advagraf astagraf calcineurin NEAR/2 inhibit* cipol 'cni' cyclokat cyclosporin cyclosporine 'CSA-neoral' 'cya-nof' deximune gengraf hecoria immunosporin implanta imusporin 'mustopic oint' neoral

Controlled Vocabulary and Keywords (continued)

Concept	Controlled Vocabulary	Keywords
	'vekacia'/exp	'ol-27-400' prograf tacrolimus tsukubaenolide vekacia
CNI Minimization	'low drug dose'/exp 'dosage schedule comparison'/exp 'treatment withdrawal'/exp 'drug withdrawal'/exp	Alternative AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) avoid* AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) eliminate* AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) low AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) lower* AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) minimize AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) minimization AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) minimal AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) reduce AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) reduction AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) taper* AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen) withdraw* AND (dose* OR dosing OR dosage* OR drug* OR strategy OR strategies OR regimen)
CNI alternative drugs	'alemtuzumab'/exp 'belatacept'/exp 'everolimus'/exp 'rapamycin'/exp 'sotrustaurin'/exp 'tofacitinib'/exp	alemtuzumab belatacept everolimus' rapamycin sirolimus sotrustaurin tofacitinib

Controlled Vocabulary and Keywords (continued)

Concept	Controlled Vocabulary	Keywords
Drug Monitoring timepoints (Cyclosporine)	NA	('area under' NEXT/1 curve) (‘2’ OR ‘two’) NEAR/1 hour* "c1" "c0" "c2" (time OR ‘time point’ OR timepoint* OR timing OR duration) AND (cyclospor* NEAR/2 level*) time NEAR/1 series trough
Drug Monitoring Terms	'area under the curve'/exp 'drug monitoring'/exp 'pharmacodynamics'/exp 'pharmacokinetics'/exp	('area under' NEXT/4 curve) bioequivalence 'drug monitoring' (drug OR therapy OR therapeutic) AND (monitor* OR measure* OR surveillance) drug NEAR/3 (clearance OR activation OR adsorp* OR absorp* OR bioavailabilit* OR distribution) (limit NEXT/3 quantification) 'loq'
Immunoassays/Mass Spectrometry	'immunoassay'/exp 'mass spectrometry'/exp 'high performance liquid chromatography'/exp	ACMIA 'antibody conjugated magnetic immunoassay' 'elisa' 'emit' 'enzyme linked immunosorbent assay' 'enzyme multiplied immunoassay' fluorescence NEAR/1 polarization 'fria' 'gc-ms' 'high performance liquid chromatography' 'hplc' 'hplc-ms' 'immunoassay' 'lc-ms' 'liquid chromatography' NEAR/2 'mass spectrometry' 'mass spectrometry' (mass NEAR/1 spectrometr*) 'meia' 'microparticle enzyme immunoassay' 'ms'
Kidney Transplantation	EMBASE (EMTREE) 'kidney graft'/exp	'kidney graft' 'kidney transplantation' 'renal graft dysfunction' (kidney OR renal) NEAR/2 (allograft* OR alograft* OR transplant* OR homograft* OR graft*)

*EMTREE terms are mapped to corresponding Medical Subject Heading (MeSH) terms in Embase.com.

Search Strategies

EMBASE/MEDLINE for Key Question 1 and Key Question 3b (presented in Embase.com syntax)

Set Number	Concept	Search Statement
1	Kidney transplantation	'kidney graft'/exp OR 'kidney graft' OR 'kidney transplantation' OR 'renal graft dysfunction'/exp OR 'renal graft dysfunction' OR (kidney OR renal) NEAR/2 (allograft* OR allograft* OR transplant* OR homograft* OR graft*)
2	Immunosuppressive drugs	'tacrolimus'/exp OR tacrolimus OR 'cyclosporin'/exp OR cyclosporin OR 'cyclosporine'/exp OR cyclosporine OR 'ciclosporine'/exp OR ciclosporine OR 'mustopic oint'/exp OR 'mustopic oint' OR 'tsukubaenolide'/exp OR tsukubaenolide OR 'cipol'/exp OR cipol OR 'cyclokat'/exp OR cyclokat OR 'deximune'/exp OR deximune OR 'implanta'/exp OR implanta OR 'immunosporin'/exp OR immunosporin OR imusporin OR 'vekacia'/exp OR vekacia OR 'prograf'/exp OR prograf OR 'advagraf'/exp OR advagraf OR 'hecoria'/exp OR hecoria OR 'neoral'/exp OR 'gengraf'/exp OR gengraf OR 'astagraf'/exp OR astagraf OR 'ol-27-400' OR 'CSA-neoral' OR 'cya-nof' OR neoral
3		'calcineurin inhibitor'/exp OR calcineurin NEAR/2 inhibit* OR 'cni'
4	Combine sets	2 or 3
5	Combine sets	1 and 4
6	Monitoring assays	'immunoassay'/exp OR immunoassay* OR 'mass spectrometry'/exp OR 'mass spectrometry' OR 'high performance liquid chromatography'/exp OR (mass NEAR/1 spectrometr*) OR 'ms' OR 'gc-ms' OR 'hplc-ms' OR 'high performance liquid chromatography' OR 'hplc' OR (fluorescence NEAR/1 polarization) OR 'fpia' OR 'enzyme multiplied immunoassay' OR 'emit' OR 'enzyme linked immunosorbent assay' OR 'elisa' OR 'microparticle enzyme immunoassay' OR 'meia' OR ('liquid chromatography' NEAR/2 'mass spectrometry') OR 'lc-ms' OR 'antibody conjugated magnetic immunoassay' OR ACMIA
7	Drug monitoring	'drug monitoring'/exp OR 'drug monitoring' OR ((drug OR therapy OR therapeutic) AND (monitor* OR measure* OR surveillance)) OR 'pharmacodynamics'/exp OR 'area under the curve'/exp OR 'pharmacokinetics'/exp OR bioequivalence OR (drug NEAR/3 (clearance OR activation OR adsorp* OR absorp* OR bioavailabilit* OR distribution)) OR ('area under' NEXT/4 curve) OR (limit NEXT/3 quantification) OR 'loq'
8	Combine sets	5 AND 6 AND 7
9	Diagnostic test Hedge	8 AND ('diagnostic accuracy'/exp OR 'diagnosis':lnk OR 'receiver operating characteristic':de OR 'roc curve'/exp OR 'roc curve' OR 'sensitivity and specificity':de OR 'sensitivity' OR 'specificity' OR 'accuracy':de OR 'precision'/exp OR 'precision':de OR 'prediction and forecasting'/exp OR 'prediction and forecasting' OR 'diagnostic error'/exp OR 'diagnostic error' OR 'maximum likelihood method':de OR 'test retest reliability'/exp OR (test NEXT/3 reliability) OR 'reliability'/exp OR 'validity'/exp OR 'measurement repeatability'/exp OR 'likelihood' OR 'predictive value'/exp OR 'predictive value' OR 'ppv' OR ((false OR true) NEAR/1 (positive OR negative)) OR ('area under' NEXT/4 curve) OR (limit NEXT/3 quantification) OR 'loq' OR ('inter assay' OR 'inter-assay' OR 'inter laboratory' OR 'inter-laboratory') NEAR/2 (agreement OR measurement OR reproducibility))

**EMBASE/MEDLINE for Key Question 1 and Key Question 3b (presented in Embase.com syntax)
(continued)**

Set Number	Concept	Search Statement
10	Clinical trials filter	8 AND ('randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR 'randomization' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'single blind procedure'/exp OR 'single blind procedure' OR 'placebo'/exp OR 'placebo' OR 'latin square design'/exp OR 'latin square design' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'controlled study'/exp OR 'controlled study' OR 'clinical trial'/exp OR 'clinical trial' OR 'comparative study'/exp OR 'comparative study' OR 'cohort analysis'/exp OR 'cohort analysis' OR 'follow up'/exp OR 'follow up' OR 'intermethod comparison'/exp OR 'intermethod comparison' OR 'parallel design'/exp OR 'parallel design' OR 'control group'/exp OR 'control group' OR 'prospective study'/exp OR 'prospective study' OR 'retrospective study'/exp OR 'retrospective study' OR 'case control study'/exp OR 'case control study' OR 'major clinical study'/exp OR 'major clinical study' OR 'evaluation study'/exp OR 'evaluation study' OR random*:de OR random*:ti OR placebo* OR (singl* OR doubl* OR tripl* OR trebl* AND (dummy OR 'blind'/exp OR blind OR sham)) OR 'latin square' OR isrcn* OR actrn* OR (nct* NOT nct))
11	Systematic Review/Meta-analysis filter	8 AND ('research synthesis' OR pooled OR 'systematic review'/exp OR 'systematic review' OR 'meta analysis'/exp OR 'meta analysis' OR ('evidence base' OR 'evidence based'/exp OR 'evidence based' OR methodol* OR systematic OR quantitative* OR studies OR search*) AND ('review'/exp OR 'review' OR 'review/it'))
12	Combine sets	9 OR 10 OR 11
13	Remove unwanted publication types	12 NOT 'book'/exp OR 'book' OR 'conference paper'/exp OR 'conference paper' OR 'editorial'/exp OR 'editorial' OR 'letter'/exp OR 'letter' OR 'note'/exp OR 'note' OR book:it,pt OR 'edited book':it,pt OR 'case report':it,pt OR 'case reports':it,pt OR comment:it,pt OR conference:it,pt OR editorial:it,pt OR letter:it,pt OR news:it,pt OR note:it,pt OR proceeding:it,pt

EMBASE/MEDLINE for Key Question 2 (presented in Embase.com syntax)

Set Number	Concept	Search Statement
1	Kidney transplantation	'kidney graft'/exp OR 'kidney graft' OR 'kidney transplantation' OR 'renal graft dysfunction'/exp OR 'renal graft dysfunction' OR (kidney OR renal) NEAR/2 (allograft* OR allograft* OR transplant* OR homograft* OR graft*)
2	Cyclosporine	Cyclosporin/exp OR Cyclosporine OR cyclosporin OR cipol OR cyclokat OR dexamune OR implanta OR imusporin OR vekacia OR ciclosporin OR 'CsA-Neoral' OR 'CyA-NOF' OR 'Neoral' OR 'OL 27-400'
3	Combine sets	1 AND 2
4	Drug monitoring/pharmacodynamics	'drug monitoring'/exp OR 'drug monitoring' OR ((drug OR therapy OR therapeutic) AND (monitor* OR measure* OR surveillance)) OR 'pharmacodynamics'/exp OR 'area under the curve'/exp OR 'pharmacokinetics'/exp OR bioequivalence OR (drug NEAR/3 (clearance OR activation OR adsorp* OR absorp* OR bioavailabilit* OR distribution)) OR ('area under' NEXT/4 curve) OR (limit NEXT/3 quantification) OR 'loq'
5	Monitoring timepoints	(('2' OR 'two') NEAR/1 hour*) OR trough OR ((time OR 'time point' OR timepoint* OR timing OR duration) AND (cyclospor* NEAR/2 level*)) OR "c1" OR "c0" OR "c2" OR ('area under' NEXT/1 curve) OR time NEAR/1 series
6	Combine sets	3 AND 4 AND 5

EMBASE/MEDLINE for Key Question 2 (presented in Embase.com syntax) (continued)

Set Number	Concept	Search Statement
7	Diagnostic test Hedge	6 AND ('diagnostic accuracy'/exp OR 'diagnosis':lnk OR 'receiver operating characteristic':de OR 'roc curve'/exp OR 'roc curve' OR 'sensitivity and specificity':de OR 'sensitivity' OR 'specificity' OR 'accuracy':de OR 'precision'/exp OR 'precision':de OR 'prediction and forecasting'/exp OR 'prediction and forecasting' OR 'diagnostic error'/exp OR 'diagnostic error' OR 'maximum likelihood method':de OR 'test retest reliability'/exp OR (test NEXT/3 reliability) OR 'reliability'/exp OR 'validity'/exp OR 'measurement repeatability'/exp OR 'likelihood' OR 'predictive value'/exp OR 'predictive value' OR 'ppv' OR ((false OR true) NEAR/1 (positive OR negative)) OR ('area under' NEXT/4 curve) OR (limit NEXT/3 quantification) OR 'loq' OR (('inter assay' OR 'inter-assay' OR 'inter laboratory' OR 'inter-laboratory') NEAR/2 (agreement OR measurement OR reproducibility))
8	Clinical Trials	6 AND ('randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR 'randomization' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'single blind procedure'/exp OR 'single blind procedure' OR 'placebo'/exp OR 'placebo' OR 'latin square design'/exp OR 'latin square design' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'controlled study'/exp OR 'controlled study' OR 'clinical trial'/exp OR 'clinical trial' OR 'comparative study'/exp OR 'comparative study' OR 'cohort analysis'/exp OR 'cohort analysis' OR 'follow up'/exp OR 'follow up' OR 'intermethod comparison'/exp OR 'intermethod comparison' OR 'parallel design'/exp OR 'parallel design' OR 'control group'/exp OR 'control group' OR 'prospective study'/exp OR 'prospective study' OR 'retrospective study'/exp OR 'retrospective study' OR 'case control study'/exp OR 'case control study' OR 'major clinical study'/exp OR 'major clinical study' OR 'evaluation study'/exp OR 'evaluation study' OR random*:de OR random*:ti OR placebo* OR (singl* OR doubl* OR tripl* OR trebl* AND (dummy OR 'blind'/exp OR blind OR sham)) OR 'latin square' OR isrcn* OR actrn* OR (nct* NOT nct))
9	Systematic Review/Meta-analysis filter	6 AND ('research synthesis' OR pooled OR 'systematic review'/exp OR 'systematic review' OR 'meta analysis'/exp OR 'meta analysis' OR ('evidence base' OR 'evidence based'/exp OR 'evidence based' OR methodol* OR systematic OR quantitative* OR studies OR search*) AND ('review'/exp OR 'review' OR 'review/it'))
10	Combine sets	7 OR 8 OR 9
11	Remove unwanted publication types	10 NOT 'book'/exp OR 'book' OR 'conference paper'/exp OR 'conference paper' OR 'editorial'/exp OR 'editorial' OR 'letter'/exp OR 'letter' OR 'note'/exp OR 'note' OR book:it,pt OR 'edited book':it,pt OR comment:it,pt OR conference:it,pt OR editorial:it,pt OR letter:it,pt OR news:it,pt OR note:it,pt OR proceeding:it,pt
12	Remove overlap from KQ1	11 NOT (results from KQ1)

EMBASE/MEDLINE for Key Question 3a (presented in Embase.com syntax)

Set Number	Concept	Search Statement
1	Kidney transplantation	'kidney graft'/exp OR 'kidney graft' OR 'kidney transplantation' OR 'renal graft dysfunction'/exp OR 'renal graft dysfunction' OR (kidney OR renal) NEAR/2 (allograft* OR allograft* OR transplant* OR homograft* OR graft*)
2	Immunosuppressive drugs	'tacrolimus'/exp OR tacrolimus OR 'cyclosporin'/exp OR cyclosporin OR 'cyclosporine'/exp OR cyclosporine OR 'ciclosporine'/exp OR ciclosporine OR 'mustopic oint'/exp OR 'mustopic oint' OR 'tsukubaenolide'/exp OR tsukubaenolide OR 'cipol'/exp OR cipol OR 'cyclokat'/exp OR cyclokat OR 'deximune'/exp OR deximune OR 'implanta'/exp OR implanta OR 'immunosporin'/exp OR immunosporin OR imusporin OR 'vekacia'/exp OR vekacia OR 'prograf'/exp OR prograf OR 'advagraf'/exp OR advagraf OR 'hecoria'/exp OR hecoria OR 'neoral'/exp OR 'gengraf'/exp OR gengraf OR 'astagraf'/exp OR astagraf OR 'ol-27-400' OR 'CSA-neoral' OR 'cya-nof' OR neoral
3		'calcineurin inhibitor'/exp OR calcineurin NEAR/2 inhibit* OR 'cni'
4	Combine sets	2 or 3
5	Combine sets	1 and 4
6	Dose minimization	'low drug dose'/exp OR 'dosage schedule comparison'/exp OR 'treatment withdrawal'/exp OR 'drug withdrawal'/exp OR ((low OR lower* OR reduce OR reduction OR minimize OR minimization OR minimal OR withdraw* OR avoid* OR eliminate* OR taper* OR alternative OR conversion) NEAR/4 (dose* OR dosing OR dosage* OR drug* OR calcineurin OR tacrolimus OR cyclosporine* OR 'CNI' OR strategy OR strategies OR regimen*))
7	CNI alternatives (major concepts)	'rapamycin'/exp/mj OR 'rapamycin':ti OR 'everolimus'/exp/mj OR 'everolimus':ti OR 'alemtuzumab'/exp/mj OR 'alemtuzumab':ti OR 'sotрастaurин'/exp/mj OR 'sotрастaurин':ti OR 'tofacitinib'/exp/mj OR 'tofacitinib':ti OR 'belatacept'/exp/mj OR 'belatacept':ti OR sirolimus:ti
8	Combine sets	5 AND (6 OR 7)
9	Controlled trials filter	8 AND ('randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR 'randomization' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'single blind procedure'/exp OR 'single blind procedure' OR 'placebo'/exp OR 'placebo' OR 'latin square design'/exp OR 'latin square design' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'triple blind procedure'/exp OR 'triple blind procedure' OR 'controlled study'/exp OR 'controlled study' OR 'clinical trial'/exp OR 'clinical trial' OR 'comparative study'/exp OR 'comparative study' OR 'cohort analysis'/exp OR 'cohort analysis' OR 'follow up'/exp OR 'follow up' OR 'intermethod comparison'/exp OR 'intermethod comparison' OR 'parallel design'/exp OR 'parallel design' OR 'control group'/exp OR 'control group' OR 'prospective study'/exp OR 'prospective study' OR 'retrospective study'/exp OR 'retrospective study' OR 'case control study'/exp OR 'case control study' OR 'major clinical study'/exp OR 'major clinical study' OR 'evaluation study'/exp OR 'evaluation study' OR random*:de OR random*:ti OR placebo* OR (singl* OR doubl* OR tripl* OR trebl* AND (dummy OR 'blind'/exp OR blind OR sham)) OR 'latin square' OR isrcrn* OR actrn* OR (nct* NOT nct))
10	Systematic Review/Meta-analysis filter	8 AND ('research synthesis' OR pooled OR 'systematic review'/exp OR 'systematic review' OR 'meta analysis'/exp OR 'meta analysis' OR ((evidence base' OR 'evidence based'/exp OR 'evidence based' OR methodol* OR systematic OR quantitative* OR studies OR search*)) AND ('review'/exp OR 'review' OR 'review/it)))
11	Combine sets	9 OR 10

EMBASE/MEDLINE for Key Question 3a (presented in Embase.com syntax) (continued)

Set Number	Concept	Search Statement
12	Remove unwanted publication types	11 NOT 'book'/exp OR 'book' OR 'conference paper'/exp OR 'conference paper' OR 'editorial'/exp OR 'editorial' OR 'letter'/exp OR 'letter' OR 'note'/exp OR 'note' OR book:it,pt OR 'edited book':it,pt OR 'case report':it,pt OR comment:it,pt OR conference:it,pt OR editorial:it,pt OR letter:it,pt OR news:it,pt OR note:it,pt OR proceeding:it,pt

Embase.com Syntax:

- * = truncation character (wildcard)
- NEAR/*n* = search terms within a specified number (*n*) of words from each other in any order
- NEXT/*n* = search terms within a specified number (*n*) of words from each other in the order specified
- / = search as a subject heading
- exp = “explodes” controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary’s hierarchy)
- mj = denotes a term that has been searched as a major subject heading
- :de = search in the descriptors field (controlled terms and keywords)
- :lnk = floating subheading
- :it,pt. = source item or publication type
- :ti. = limit to title
- :ti,ab. = limit to title and abstract fields

PUBMED (PreMEDLINE) for Key Question 1 and Key Question 3b

Set Number	Concept	Search Statement
1	Kidney transplantation	(kidney OR renal) AND (allograft* OR alograft* OR transplant* OR homograft* OR graft*)
2	Immunosuppressive drugs	tacrolimus OR cyclosporin OR cyclosporine OR ciclosporine OR "mustopic oint" OR tsukubaenolide OR cipol OR cyclokat OR dexamune OR implanta OR immunosporin OR imusporin OR vekacia OR prograf OR advagraf OR hecoria OR gengraf OR astagraf OR "ol-27-400" OR "CSA-neoral" OR "cya-nof" OR neoral
3		(calcineurin AND inhibit*) OR "cni"
4	Combine sets	2 or 3
5	Combine sets	1 and 4
6	Immunoassay/ Mass Spectrometry	immunoassay* OR "mass spectrometry" OR "high performance liquid chromatography" OR (mass AND spectrometr*) OR "gc-ms" OR "hplc-ms" OR "hplc" OR (fluorescence AND polarization) OR "fpia" OR "enzyme multiplied immunoassay" OR "emit" OR "enzyme linked immunosorbent assay" OR "elisa" OR "microparticle enzyme immunoassay" OR "meia" OR ("liquid chromatography" AND "mass spectrometry") OR "lc-ms" OR "antibody conjugated magnetic immunoassay" OR "ACMIA"
7	Combine sets	5 AND 6
8	Remove unwanted publication types	7 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
9	Limit to in process citations	10 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])

PUBMED (PreMEDLINE) for Key Question 2

Set Number	Concept	Search Statement
1	Kidney transplantation	(kidney OR renal) AND (allograft* OR alograft* OR transplant* OR homograft* OR graft*)
2	Immunosuppressive drugs	cyclosporine OR cyclosporin OR cipol OR cyclokat OR dexamune OR implanta OR imusporin OR vekacia OR ciclosporin OR "CsA-Neoral" OR "CyA-NOF" OR "Neoral" OR "OL 27-400"
3	Combine sets	1 AND 2
4	Monitoring time points	(("2"[tiab] OR two[tiab]) AND hour*) OR trough OR ((time OR "time point" OR timepoint* OR timing OR duration) AND cyclospor* AND level*) OR "c1"[tiab] OR "c0"[tiab] OR "c2"[tiab] OR "area under the curve" OR "time series"
5	Combine sets	3 AND 4
6	Remove unwanted publication types	5 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
9	Limit to in process citations	6 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])

PUBMED (PreMEDLINE) for Key Question 3a

Set Number	Concept	Search Statement
1	Kidney transplantation	(kidney OR renal) AND (allograft* OR allograft* OR transplant* OR homograft* OR graft*)
2	Immunosuppressive drugs	tacrolimus OR cyclosporin OR cyclosporine OR ciclosporine OR "mustopnic oint" OR tsukubaenolide OR cipol OR cyclokat OR dexamune OR implanta OR immunosporin OR imusporin OR vekacia OR prograf OR advagraf OR hecoria OR gengraf OR astagraf OR "ol-27-400" OR "CSA-neoral" OR "cya-nof" OR neoral
3		(calcineurin AND inhibit*) OR "cni"
4	Combine sets	2 or 3
5	Combine sets	1 and 4
6	Dose minimization	(low[tiab] OR lower*[tiab] OR reduce[tiab] OR reduction[tiab] OR minimize[tiab] OR minimization[tiab] OR minimal[tiab] OR withdraw*[tiab] OR avoid*[tiab] OR eliminate*[tiab] OR taper*[tiab] OR alternative[tiab] OR conversion[tiab]) AND (dose*[tiab] OR dosing[tiab] OR dosage*[tiab] OR calcineurin[tiab] OR tacrolimus[tiab] OR cyclosporine*[tiab] OR 'CNI'[tiab] OR strategy[tiab] OR strategies[tiab] OR regimen*[tiab])
7	CNI Alternatives	rapamycin OR everolimus OR alemtuzumab OR sotraxtaurin OR tofacitinib OR belatacept OR sirolimus
8	Combine sets	5 AND (6 OR 7)
9	Remove unwanted publication types	8 NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt])
10	Limit to in process citations	9 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])
11	Controlled trials filter	10 AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR meta-analysis[mh] OR meta-analysis[pt] OR outcomes research[mh] OR multicenter study[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw])) AND (mask*[tw] OR blind*[tw])) OR "latin square" OR placebos[mh] OR placebo* OR random* OR "control group" OR prospective* OR retrospective* OR volunteer* OR sham OR "meta-analysis"[tw] OR cohort OR ISRCTN* OR ACTRN* OR NCT*)
12	Systematic Review/Meta-analysis filter	10 AND (meta-analysis OR meta-analysis[pt] OR ((evidence base* OR methodol* OR systematic* OR quantitativ* OR studies OR overview* OR search) AND review[pt]))
13	Combine sets	11 OR 12

PubMed Syntax:

* = truncation character (wildcard)

[ti] = limit to title field

[tiab] = limit to title and abstract fields

[tw] = text word

Appendix B. Excluded Studies

Does not meet study design criteria (e.g., not a randomized controlled trial, previous systematic review, narrative review or commentary)

An open label, prospective, randomized, controlled, multi-center study assessing fixed dose vs concentration controlled CellCept regimens for patients following a single organ renal transplantation in combination with full dose and reduced dose calcineurin inhibitors. *Dev Behav Pediatr Online.* 2004. Also available: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/645/CN-00487645/frame.html>.

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Appendix C. Evidence Tables for Key Question 1a and 1b

Table C-1. Study characteristics

Reference	Country	Type of Study Study Design (n)	CNI Regimen	Intervention Monitoring Method	Comparative/Reference Monitoring Method	Outcomes	Follow-up
Leung et al. 2014 ²⁶	USA	Analytical accuracy of tests measuring TAC , prospective comparative study (145)	TAC regimen	QMS TAC immunoassay (QMS)	LC-MS/MC (in house)	Analytical performance	Not reported
Shipkova et al. 2014 ²⁷	Germany	Analytical accuracy of tests measuring TAC, prospective comparative study (60)	TAC regimen	Elecsys TAC assay (ELCIA)	LC-MS/MC	Analytical performance	Not reported
Westley et al. 2007 ²⁸	Australia	Analytical accuracy of tests measuring TAC, retrospective comparative study (67)	TAC regimen	CEDIA and MEIA	HPLC-MS	TAC concentrations and analytical performance	Not reported
Borrows et al. 2006 ²⁵	United Kingdom	Clinical utility of test measuring TAC, RCT (80)	TAC (10-15 ng/ml)+ MMF (750 mg/twice daily) and induction anti-CD25 monoclonal	HPLC-MS	MEIA	Patient and graft survival, graft function, BPAR, bacterial infection, incidence of CMV, NODM, other adverse events; inter-assay variability	6 months
Chan et al. 2005 ²⁹	China	Analytical accuracy of tests measuring TAC, prospective comparative study (30)	TAC+ prednisolone and AZA	HPLC-MS	MEIA	TAC concentration, analytical performance, clinical management	Not reported
Staatz et al. 2002 ³⁰	Australia	Analytical accuracy of tests measuring TAC, retrospective comparative study (76)	TAC+ MMF or AZA and steroids	LC/MS/MS	ELISA	TAC concentrations and analytical performance	Data collected from patients who received either a liver or kidney transplant from 1994 to 2000
Salm et al. 1997 ³¹	Australia	Analytical accuracy of tests measuring TAC. prospective comparative study (67)	TAC regimen	ELISA and MEIA	HPLC-MS ² Developed by the authors of the study; HPLC-MS tandem mass spectrometry	TAC concentrations and analytical performance	4 months

BPAR=biopsy proven acute rejection; CEDIA=cloned enzyme donor immunoassay; CMV=cytomegalovirus; CsA=cyclosporine; ELCIA=electrochemiluminescence immunoassay; ELISA=enzyme-linked immunosorbent assay; FPIA=fluorescence polarization immunoassay; HPLC-MS=high performance liquid chromatography; LC/MS/MS=liquid chromatography-tandem mass spectrometry; MEIA=microparticle enzyme immunoassay; MMF=mycophenolate mofetil; NODM=new onset diabetes mellitus; RCT=randomized controlled trial; RIA=radio-immunoassay; TAC=tacrolimus

Table C-2. Patient characteristics

Reference	Number of Patients	Mean Age	Percent Male	Number Live Donor Recipients	Percent Ethnicity
Shipkova et al. 2014 ²⁷	60 patients who underwent kidney transplant (other patient in the study underwent heart and liver transplants)	Not reported	Not reported	Not reported	Not reported
Leung et al. 2014 ²⁶	145 whole blood samples	Not reported	Not reported	Not reported	Not reported
Westley et al. 2007 ²⁸	88 patients who underwent kidney transplant (other patients in study underwent liver transplant)	Range: 9 to 69 years	66%	Not reported	Not reported
Borrows et al. 2006 ²⁵	MEIA: 40 HPLC: 40 All patients underwent kidney transplant	MEIA: 46 years HPLC: 44 years	MEIA: 65% HPLC-MS: 45%	MEIA: 18 HPLC-MS: 19	MEAI: 45% Caucasian, 25% Indo-Asian, 20% Afro-Caribbean, 5.0% Mid-Eastern, 5.0% Asian HPLC-MS: 60% Caucasian, 22% Indo-Asian, 17% Afro-Caribbean, 0% Mid-Eastern and Asian
Chan et al. 2005 ²⁹	30 patients; all patients underwent kidney transplant	42.6 years	53%	Not reported	Not reported
Staatz et al. 2002 ³⁰	76 patients who underwent kidney transplant (other patients in study underwent liver transplant)	Patients aged 15 years or older	Not reported	Not reported	Not reported
Salm et al. 1997 ³¹	37 patients who underwent kidney transplant (other patients in study underwent liver transplant)	No reported	Not reported	Not reported	Not reported

HPLC-MS=high performance liquid chromatography; MEIA=microparticle enzyme immunoassay

Table C-3. Primary findings of study measuring clinical utility

Reference	Number of Patients	Follow-up	TAC Level (ng/ml)	Patient Survival	Graft Survival	BPAR	DGF	TAC Nephrotoxicity	Serum Creatinine (µmol/l)
Borrows et al. 2006 ²⁵	MEIA: 40 HPLC-MS: 40	6 months	MEIA: 11.1±2.7 HPLC: 9.2±2.3 (p=0.02)	MEIA: 100% HPLC-MS: 100%	MEIA: 100% HPLC-MS: 97.5%	MEIA: 4 patients (10%) HPLC-MS: 1 patient (2.5%) No significant difference (p=0.17)	MEIA: 14 patients (35%) HPLC-MS: 12 patients (30%) No significant difference	MEIA: 6 patients (15%) HPLC-MS: 7 patients (17.5%)	MEIA: 142±39 HPLC-MS: 141±45 No significant difference

BPAR=biopsy proven acute rejection; DGF=delayed graft function; HPLC-MS=high performance liquid chromatography-mass spectrometry; MEIA=microparticle enzyme immunoassay; TAC=tacrolimus

Table C-4. Analytical validity outcomes

Reference	Number of Patients (blood samples)	Method Comparison	Sampling Procedure	CNI Concentration	Correlation Between Methods	Limits of Agreement	Difference in AUC ₁₂ Values	Mean Bias	Precision
Leung et al. 2014 ²⁶	145 whole blood samples	QMS TAC immunoassay (QMS) vs. LC-MS/MS (in house)	Whole blood samples collected from patients undergoing routine TAC monitoring; samples stored at below -20 C until tested.	Not reported	r ² =0.99 Slope 1.13 (range 4.0 to 84.6 ng/mL)	NR	NR	31% (overall per Bland/Altman analysis = 2.4 ng/mL)	Coefficient of variance for intra-assay and inter-assay precision studies ranged from 3.9% to 8.1% and 4.7% to 10.0%.
Shipkova et al. 2014 ²⁷	60 whole blood	Elecsys TAC assay (ELCIA) vs. LC-MS/MC	Blood samples collected from 5 different sites; samples stored at room temperature if tested within 8 hours of collection or at below -15 C if tested at a later time; all samples were measured within 6 months of collection.	Slope 1.0±0.10, intercept <1/10 of the low end of the therapeutic concentration range of 3.0 µg/L for kidney	r ² =0.97 Slope: 1.13 (95% CI: 1.09 to 1.16 According to the authors, this value fell out of the acceptance value of 1.0±0.1	NR	NR	5.9% (95% CI: -27.8% to -39.5%)	For ELCIA only: Linearity: 0.5 to 40 µg/L; functional sensitivity: 0.3 µg/L (CV≤20%) Intermediate imprecision for TAC concentration ≥6.8 µg/L was ≤6.5% Lower imprecision for TAC to 1.5 µg/L was consistently ≤10%

Table C-4. Analytical validity outcomes (continued)

Reference	Number of Patients (blood samples)	Method Comparison	Sampling Procedure	CNI Concentration	Correlation Between Methods	Limits of Agreement	Difference in AUC ₁₂ Values	Mean Bias	Precision
Westley et al. 2007 ²⁸	88 (88) Samples underwent approximately three freeze/thaw cycles during the study period between the two study centers.	CEDIA and MEIA vs. HPLC-MS	NR	See precision data	CEDIA vs. HPLC-MS: $r^2=0.77$ CEDIA vs. MEIA: $r^2=0.72$ MEIA vs. HPLC-MS: $r^2=0.90$	NR	NR	CEDIA vs. HPLC-MS: 33.3% (± 3.9) CEDIA vs. MEIA: 13.9% (± 4.4) MEIA vs. HPLC-MS: 20.1 (± 2.5)%	CEDIA vs. HPLC-MS: RMSE=5.7 $\mu\text{g/L}$ CEDIA vs. MEIA: RMSE=3.7 $\mu\text{g/L}$ MEIA vs. HPLC-MS: RMSE=2.8 $\mu\text{g/L}$
Borrows et al. 2006 ²⁵	40 (total samples not reported)	HPLC-MS vs. MEIA	TAC levels measured daily from first day post-transplant to discharge from hospital and at each clinic visit	Median/Range TAC at 6 months: MEIA: 12.8 (6.7 to 22.0) $\mu\text{g/ml}$ HPLC-MS: 9.9 (5.5 to 18.9) $\mu\text{g/ml}$	NR	NR	NR	NR	Inter-assay variability at 5, 11, and 22 $\mu\text{g/ml}$ TAC: MEIA 13.7%, 8.3%, 10.9% HPLC 8.0%, 6.5%, 5.7%
Chan et al. 2005 ²⁹	30 (134)	HPLC-MS vs. MEIA	50 pairs of 2-hour post-dose (C2) and 4-hour post-dose (C4) were used; with an estimation of the 12-hour AUC done using a two-point sampling method; TAC concentrations measured at a median 13.5 months post-transplant	HPLC-MS: median TAC 9.75 (7.08) $\mu\text{g/L}$ MEIA: 10.30 (8.08) $\mu\text{g/L}$ Median difference -0.40 (2.03) $\mu\text{g/L}$; $p<0.001$; % difference 5.04%; concentrations significantly, but not clinically, lower for HPLC-MS	$r^2=0.94$; $p<0.001$; indicates good correlation between methods	95% LoA 2.98 to -4.10 $\mu\text{g/L}$; 90% of patients had an absolute difference of less than 3.1 $\mu\text{g/L}$	Mean difference: 3.4 \pm 11.6 hr. $\mu\text{g/L}$; $p=0.059$; % difference 2.6 \pm 11.4%; $p=0.107$	NR	NR

Table C-4. Analytical validity outcomes (continued)

Reference	Number of Patients (blood samples)	Method Comparison	Sampling Procedure	CNI Concentration	Correlation Between Methods	Limits of Agreement	Difference in AUC ₁₂ Values	Mean Bias	Precision
Staatz et al. 2002 ³⁰	29 (98)	LC/MS/MS vs. ELISA	12-hour trough monitoring; immediate post-transplant and subsequent at each clinical visit. Samples for concentration monitoring ranged from 2 to 402 days post-transplant; samples per subject ranged from 1 to 6 (median 4)	ELISA TAC ranged from 1.9 to 43.4 ng/mL LC/MS/MS ranged from 1.7 to 44 ng/mL	r ² =0.95; SE.EST: 1.37	NR	NR	ELISA vs. LC/MS/MS 0.47 (\pm 1.37) At TAC 0 to 6 ng/ml, Mean Bias: 4.7 (\pm 19.6)	Relative difference between 2 assays at 5, 10, and 20 ng/ml TAC: Reported as 95% CIs: -50% to 60%, -24% to 31%, and -11% to 17%
Salm et al. 1997 ³¹	37 (129)	ELISA and MEIA vs. HPLC-MS2 Developed by the authors of the study; HPLC-MS tandem mass spectrometry	12-hour trough monitoring; first sample within 1 week of transplant; additional samples collect each month for 4 months	HPLC-MS2 TAC ranged from 1.7 to 26.1 μ g/l; ELISA ranged from 1.9 to 24.4 μ g/l; MEIA 0.9 to 28.5 μ g/l	ELISA vs. HPLC-MS: SE. EST 1.26; MEIA vs. HPLC-MS: SE.EST 2.13	NR	NR	ELISA vs. HPLC-MS: 0.171 (\pm 1.27) MEIA vs. HPLC-MS: 1.78 (\pm 2.24)	Relative difference between assays at 5, 10, 20 μ g/l TAC: Reported as 95% CIs: ELISA vs. HPLC-MS 2.9 to 7.9, 7.7 to 12.7, and 17.2 to 22.2 MEIA vs. HPLC-MS 1.7 to 10.2, 7.5 to 16.0, 19.2 to 27.6

AUC=area under the curve; CEDIA=cloned enzyme donor immunoassay; CI=confidence interval; CMIA=chemiluminescent microparticle immunoassay; CsA=cyclosporine; CV=coefficients of variance; ELCIA=electrochemiluminescence immunoassay; ELISA=enzyme-linked immunosorbent assay; FPIA=fluorescence polarization immunoassay; HPLC=high performance liquid chromatography; LC-MS/MS=liquid chromatography-mass spectrometry; LC/MS/MS=liquid chromatography-tandem mass spectrometry; LoA=limits of agreement; HPLC-MS=high performance liquid chromatography-mass spectrometry; MEIA=microparticle enzyme immunoassay; ng/mL=nanogram/milliliter; NR=not reported; RMSE=root mean squared error; SE. EST=standard error of the estimate; TAC=tacrolimus; μ g/l=micrograms per liter

Table C-5. Adverse events

Reference	Number of Patients	Bacterial Infection	Cytomegalovirus	Biopsy Proven Nephrotoxicity	New Onset Diabetes	Tremor
Borrows et al. 2006 ²⁵	MEIA: 40 HPLC-MS: 40	MEAI: 11 patients (32.5%) HPLC-MS: 11 patients (32.5%)	MEIA: 2 patients (5.0%) HPLC-MS: 0 patients	MEAI: 6 (15%) HPLC-MS: 7 (17.5%)	MEIA: 1 patient (2.5%) HPLC-MS: 0 patients	MEIA: 2 patients (5.0%) HPLC-MS: 2 patients (5.0%)

HPLC=high performance liquid chromatography mass spectrometry; MEIA=microparticle enzyme immunoassay

Table C-6. Risk of bias assessment of clinical outcomes

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar in terms of demographic and clinical factors (e.g. kidney function) at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which the patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Overall Risk of Bias
Borrows et al. 2006 ²⁵	NR	NR	Yes	Yes	NR	NR	Yes	Yes	Yes	Low

NR=not reported

Table C-7. Risk of bias assessment of analytical validity studies

Author, Year	Were the tests under evaluation described in sufficient detail to permit replication of the tests?	Were the testing results interpreted by blinded interpreters?	Was the limit of detection of the test reported?	Was the assay linearity range reported?	Has the issue of cross-reactivity been thoroughly evaluated?	Was the reproducibility of the test when performed multiple times on a single specimen established?	Was the reproducibility of the test adequately established (across operators/instruments/reagent lots/different days of the week/different laboratories)?	Were the study data from a multisite collaborative, proficiency testing, or interlaboratory exchange programs?
Leung et al. 2014 ²⁶	Yes	NR	Yes	Yes	NR	Yes	Yes	No
Shipkova et al. 2014 ²⁷	Yes	NR	No	Yes	NR	Yes	Yes	Yes
Westley et al. 2007 ²⁸	Yes	NR	Yes	Yes	NR	Yes	NR	No
Chan et al. 2005 ²⁹	Yes	NR	Yes	No	NR	NR	NR	No
Staatz et al. 2002 ³⁰	No	NR	No	No	NR	NR	NR	No
Salm et al. 1997 ³¹	Yes	NR	No	No	NR	NR	NR	No

Appendix D. Evidence Tables for Key Question 2

Table D-1. Study characteristics

Reference	Country	Type of Study (n)	Immunosuppressive Regimen	Monitoring Procedure	Assay Type	Target CNI Level	Outcomes	Follow-up
Kyllonen & Salmela 2006 ³³	Finland	RCT (154)	CsA, steroids and MMF	Patients randomized to C0 or C2 monitoring for first 3 weeks post-transplant; C0 monitoring only starting week 4	FPIA	By day 5 post-transplant C0 250 µg/mL (range 200 to 300) C2 1,700 µg/mL (range 1,500 to 2,000)	C0 and C2 levels, serum creatinine, BPAR, and adverse events	12 months
Paydas et al. 2005 ³⁴	Turkey	Retrospective comparative trial (37)	CsA, prednisone and MMF or AZA	C0 and C2 levels evaluated local hospital from month 1 to month 36 post-transplant; C2 blood samples taken 2 hours ±15 mins	Cobas Integra (Roche)	C0 after 1 year: <200 ng/mL C2 after 1 year: 800 ng/mL	C0 and C2 levels, serum creatinine levels, creatinine clearance levels, cholesterol	36 months
Praditpornsilpa et al. 2005 ³⁵	Thailand	Historically controlled comparative trial (210)	C0 group: CsA and steroids (100%), AZA (60.2%) or MMF (39.8%) C2 group: CsA and steroids (100%), AZA (79.5%), MMF (20.5%)	NR	NR	CsA C0 at 12 and 24 months: 220±42 and 167±44 ng/mL CsA C2 at 12 and 24 months: 1,000±177 and 814±15 ng/mL	C0 and C2 levels, serum creatinine level and incident of BPAR	24 months
Birsan et al. 2004 ³⁶	Austria	Historically controlled comparative trial (177)	CsA, steroids and MMF	89 patients managed prospectively by C2 monitoring; blood collected daily at 2 hours post morning dose Patients compared retrospectively to 88 patients managed by C0 monitoring	FPIA	CsA C0: 250±50 ng/mL CsA: 1,500±200ng/mL	BPAR, time to first rejection, incidence of delayed graft function, and discontinuation of study protocol	30 days and 12 months (for some outcomes)
Hardinger et al. 2004 ³⁷	USA	Prospective, non-randomized comparative trial (100)	CsA, steroids and MMF or AZA	NR	FPIA	CsA C2: 1,000 to 1,200 ng/mL months 0 to 3 and 600 to 1,000 ng/mL thereafter CsA C0: 250 to 350 ng/mL months 0 to 3 and 100 to 250 thereafter	BPAR, renal function, infection, adverse events, and drug costs	6 months

Table D-1. Study characteristics (continued)

Reference	Country	Type of Study (n)	Immunosuppressive Regimen	Monitoring Procedure	Assay Type	Target CNI Level	Outcomes	Follow-up
Jirasiritham et al. 2003 ³²	Thailand	RCT	CsA regimen	Blood CsA levels monitored bi-weekly	NR	CsA C2: 800 ng/mL with 10% variation CsA C0: 100 to 150 ng/mL	BPAR, nephrotoxicity, need for CsA dose adjustment	3 months

AUC=area under the curve; AZA=azathioprine; BPAR=biopsy proven acute rejection; C0=CsA trough level; C2=2 hour post CsA dosage level; C3=3 hour post CsA dosage level; CNI=calcineurin inhibitor; CsA=cyclosporine; EMIT=enzyme multiplied immunoassay technique; FPIA=fluorescence polarization immunoassay; MMF=mycophenolate mofetil group; NR=not reported; RCT=randomized controlled trial; µg·h/L=micrograms per hour per liter

Table D-2. Study inclusion/exclusion criteria

Reference	Inclusion Criteria	Exclusion Criteria
Kyllonen & Salmela 2006 ³³	Adult renal transplant recipients using CsA	Patients who had lost their previous graft within one year for immunologic reasons
Paydas et al. 2005 ³⁴	Adult renal transplant recipients using CsA	Not reported
Praditpornsilpa et al. 2005 ³⁵	Adult renal transplant recipients using CsA	Patients who had vascular or urologic complications post-transplantation.
Birsan et al. 2004 ³⁶	Adult patients who received their first kidney transplant from a cadaveric donor	Multi-organ transplant, human leukocyte antigen-identical donor, kidney from a non-heart beating donor, panel reactive antibody level higher than 50% at any time or higher than 30% at the time of transplantation and the need for plasmapheresis
Hardinger et al. 2004 ³⁷	Adult renal recipients receiving triple immunosuppression with CsA	Patients with a known allergy to CsA or documentation of malignancy within 2 years, with the exception of skin malignancies. Pregnant women or nursing mothers, women of childbearing years not practicing a reliable form of birth control and patients with active infection

ALG=antilymphocyte globulin; ATG=antithymocyte globulin; CsA=cyclosporine; OKT3=orthoclone; PRA=panel reactive antibody

Table D-3. Patient characteristics

Reference	Number of Patients	Mean Age	Percent Male	Percent White	Weight	Percent Live Donor Recipients	Time Since Transplant	Prior Transplant
Kyllonen & Salmela 2006 ³³	160 (C0 80 and C2 74)	C0: 51.4 years C2: 49.7 years	C0: 67.5% C2: 71.2%	NR	C0: 72.0 kg C2: 74.9 kg	0%	NR	C0: 2 patients re-transplantation C2: 3 patients re-transplantation
Paydas et al. 2005 ³⁴	37 (C0 25; C2 12)	C0: 32.3 years C2: 35.0 years	C0: 72% C2: 75%	NR	NR	C0: 84% C2: 83%	36 months	NR
Praditpornsilpa et al. 2005 ³⁵	210 (C0 128; C2 82)	C0: 40.8 years C2: 43.1 years	C0: 54.7% C2: 60.3%	All Asian	NR	C0: 28.9% C2: 29.2%	NR	NR
Birsan et al. 2004 ³⁶	177 (C0 88; C2 89)	C0: 48.9 years C2: 51.4 years	C0: 64.8% C2: 68.6%	NR	NR	100%	NR	NR
Hardinger et al. 2004 ³⁷	100 (C0 50; C2 50)	C0: 43 years C2: 51 years	C0: 62% C2: 70%	C0: 86% C2: 84%	C0: 82 kg C2: 86 kg	C0: 48% C2: 40%	NR	C0: 86% first transplant C2: 94% first transplant
Jirasiritham et al. 2003 ³²	70 (C0 35; C2 35)	NR	NR	NR	NR	NR	NR	NR

Note: The authors of Jirasiritham et al. reported no significant between group differences in the demographic profiles including: age, sex, donor type, previous episode of acute rejection, CsA nephrotoxicity, duration after kidney transplantation, and basic maintenance immunosuppressants. CsA=cyclosporine; C0=CsA trough level; C2=2 hour post CsA dosage level; kg=kilogram; NR=not reported

Table D-4. Primary clinical outcomes

Reference	Number of Patients	Mean Baseline CNI Level	Followup Mean CNI Level	Percent Above/Below Target Level CNI	Patient and Graft Survival	Mean Serum Creatinine	Graft Dysfunction	Mean Total Cholesterol
Kyllonen & Salmela 2006 ³³	160 (C0 80; C2 74)	NR	Over 21 days: CsA C0 level: 235 (224 to 245) µg/mL CsA C2 level: 1,645 (1,574 to 1,716) µg/mL Mean CsA dose: C0 4.9 mg/kg C2 7.6 mg/kg	NR	At 12 months: C0: 98.7% patient, 92.5% graft C2: 100.0% patient, 94.6% graft	Mean at 3 months: C0: 107.1 µmol/L C2: 109.2 µmol/L	Total BPAR C0: 6 patients (7.5%) and C2: 8 patients (10.8%); no difference in CsA level between rejectors and non- rejectors; DGF C0: 25 (31%); C2: 23 (31%)	NR
Paydas et al. 2005 ³⁴	37 (C0 25; C2 12)	C0: 251.44±143.33 ng/mL C2: 1,382.85±536.29 ng/mL	At 36 months: C0: 128.03±69.49 ng/mL C2: 715.84±226.58 ng/mL p<0.001	NR	NR	Baseline: C0: 1.17±0.32 mg/dL C2: 0.97±0.29 At 36 months: C0: 1.46±0.52 C2: 0.99±0.13; p=0.039 CrCl – Baseline: C0: 72.32±23.10 mL/min C2: 78.73±22.42 At 36 months: C0: 55.15±19.21 C2: 84.65±14.97 (p<0.001)	CAN developed in 13 C0 patients and 1 C2 (p=0.013)	At 36 months: C0: 234.94±48.93 C2: 206.57±38.08

Table D-4. Primary clinical outcomes (continued)

Reference	Number of Patients	Mean Baseline CNI Level	Followup Mean CNI Level	Percent Above/Below Target Level CNI	Patient and Graft Survival	Mean Serum Creatinine	Graft Dysfunction	Mean Total Cholesterol
Praditpornsilpa et al. 2005 ³⁵	210 (C0 128; C2 82)	C0: 332±109 ng/mL C2: 1,447±208 ng/mL	C0:167±44 ng/mL C2: 814±115 ng/mL	NR	NR	At 6 months, patients with C2 level >1,300 ng/mL had higher serum creatinine levels than patients with C2 <1,100 ng/mL (1.96±0.29 vs. 1.37±0.34, p<0.001); no significant differences at months 12 and 24	BPAR: C0: 7 (6.0%) C2: 9 (10%), no significant difference	NR
Birsan et al. 2004 ³⁶	177 (C0 88; C2 89)	Level not reported	Level not reported Mean daily dose 1.7 to 2.0 times higher in C2 group compared to C0 group	At followup (30 days): 10.11% of patients did not reach target CsA (1,500 ng/mL)	100% for patient and graft in both groups	No significant difference in serum creatinine at 30 days post-transplant; at one year no significant difference in mean creatinine clearance	C0: 45.4% (n=40) pts. Received treatment for rejection; C2: 28.1% (n=25) received treatment (p=0.017) Banff grade I or higher: C0: 20.45%; C2:13.48% (p=0.318)	NR
Hardinger et al. 2004 ³⁷	100 (C0 50; C2 50)	At 1 month: C0: 289±126 mg/dL C2: 1,141±316 mg/dL Significant difference (p<0.05)	At 3 months: C0: 177±60 mg/dL C2: 805±mg/dL At 6 months: C0: 160±60 mg/dL C2: 575±202 mg/dL Dose at 6 months: C0: 273± mg/dL C2: 199±73 mg/dL Significant difference (p<0.001)	NR	100% patient and graft for both groups	At 6 months: C0: 1.5±0.5 mg/dL C2: 1.5±0.6 mg/mL	C0: 3 patients experienced rejections (6.0%) C2: 2 patients experienced rejection (4.0%)	At baseline: C0: 160±46 C2: 170±44 At 6 months: C0: 177±35 C2: 191±48

Table D-4. Primary clinical outcomes (continued)

Reference	Number of Patients	Mean Baseline CNI Level	Followup Mean CNI Level	Percent Above/Below Target Level CNI	Patient and Graft Survival	Mean Serum Creatinine	Graft Dysfunction	Mean Total Cholesterol
Jirasiritham et al. 2003 ³²	70 (C0 35; C2 35)	Conversion to C2: CsA C0: 128 ng/mL C0 only: CsA C0: 156 ng/mL	C2 after conversion: 856 ng/mL C0: 137 ng/mL	C2 group: 12 (34.3%) patients needed reductions in CsA dosage and 2 (5.7%) needed increases to obtain the C2 target level; vs. C0 group: 17 (49%) needed increases in dose and 5 (15%) decreases in dose; $p=0.02$	100% both groups	NR	Group 1 (C2) 0 BPAR; Group 2 C0 only) 1 BPAR 0 Nephrotoxicity in both groups	NR

BPAR=biopsy proven acute rejection; C0=CsA trough level; C2=2 hour post CsA dosage level; C3=3 hour post CsA dosage level; Cr/Cl=creatinine clearance; CsA=cyclosporine; DGF=delayed graft function; mg/Dl=milligrams per deciliter; mL/min=milliliter per minute; ng/mL=nanogram per milliliter; NR=not reported; μ g/L=micrograms per liter; μ g/mL=micrograms per milliliter; μ mol/L=micromoles per liter

Table D-5. Adverse events and withdrawal

Reference	Adverse Events	Withdrawal or Discontinuation of CNI
Kyllonen & Salmela 2006 ³³	No difference between C0 and C2 for infections, vomiting, heartburn, upper and lower gastrointestinal symptoms, headache, diarrhea, vertigo, fatigue, insomnia, neurological symptoms, cardiac symptoms, or NODM Significantly more patients in C2 group (9) compared to C0 (2) experienced tremor ($p<0.05$)	5 patients withdrew due to discomfort with repeated blood samples
Birsan et al. 2004 ³⁶	NR	16.8% (25 patients) in C2 group and 11.4% (10 patients) in C0 group switched to tacrolimus due to acute rejection (n=17), CsA toxicity (n=8), slow/low absorbers (n=5) or other (n=5)
Hardinger et al. 2004 ³⁷	No serious fungal or viral infections (including CMV) during study period; NODM occurred in 1 patient in each group, and 20% of patients in C2 group and 27% in C0 group required treatment of new onset hypercholesterolemia	14% (7 patients) in C2 group switched to TAC (3 hirsutism, 2 hemolytic uremic syndrome, and 2 acute rejection); 10% (5 patients) switched to TAC in C0 group (2 for hirsutism and 3 for acute rejection)

C0=CsA trough level; C2=2 hour post CsA dosage level; C3=3 hour post CsA dosage level; CMV=cytomegalovirus; CNI=calcineurin inhibitor; CsA=cyclosporine; NODM: new onset diabetes mellitus; NR=not reported; TAC=tacrolimus

Table D-6. Risk of bias assessment for RCTs addressing Key Question 2

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar in terms of demographic and clinical factors (e.g., kidney function) at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment $\geq 85\%$ in both study groups?	Were outcome assessors blinded to the group to which the patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a $\leq 15\%$ difference in completion rates in the study groups?	Overall Risk of Bias
Kyllonen & Salmela 2006 ³³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Low
Jirasiritham et al. 2003 ³²	NR	NR	Yes	NR	Yes	NR	Yes	Yes	NR	Low

NR=not reported

Table D-7. Risk of bias assessment for non-randomized comparative trials addressing Key Question 2

Author, Year	Did the study employ any other methods to enhance group comparability?	Was the process of assigning patients to groups made independently from physician and patient preference?	Were groups similar in terms of demographic and clinical factors (e.g., kidney function) at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was the comparison of interest prospectively planned?	Was compliance with treatment ≥85% in both study groups?	Were outcome assessors blinded to the group to which the patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study groups?	Overall Risk of Bias
Paydas et al. 2005 ³⁴	No	No	Yes	NR	No	Yes	No	Yes	Yes	Yes	Low
Praditpornsilpa et al. 2005 ³⁵	No	No	Yes	NR	No	Yes	No	Yes	Yes	Yes	Low
Birsan et al. 2004 ³⁶	No	No	Yes	NR	Yes	Yes	No	Yes	Yes	No	Low
Hardinger et al. 2004 ³⁷	No	No	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Low

NR=not reported

Appendix E. Evidence Tables for Key Question 3a and 3b

Table E-1. Study design characteristics of minimization studies

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Cai et al. 2014 ⁴⁴	Minimization of CsA	CsA (75–90 ng/mL, C2 target 350–400 ng/mL) + EC-MPS (1,440 mg) + STER (5 mg)	CsA (150–180 ng/mL, C2 target 700–800 ng/mL) + EC-MPS (1,440 mg) + STER (5 mg)	NR	NR	3 days	Excluded age>72, PRA >20%
Chadban et al. 2014 ²³	Minimization of CsA	CsA (50% reduction from baseline) + EVR (6–10 ng/mL) + withdrawal of EC-MPS and STER	CsA (C2 target 500–700 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	2 weeks	Excluded age>65, PRA >50%, retransplants
Muhlbacher et al. 2014 ⁵⁹	Minimization of CsA	CsA (75–100 ng/mL) + SRL (4–12 ng/mL) + STER	CsA (150–200 ng/mL) + SRL (4–12 ng/mL)+ STER	IA	NR	1 month	Excluded PRA >50%, African-Americans
Oh et al. 2014 ⁶²	Minimization of CsA	CsA (25–50 ng/mL) + EVR (3–8 ng/mL) + STER (prednisolone ≥5 mg)	CsA (100–200 ng/mL) + EC-MPS (720–1,440 mg) + STER (prednisolone ≥5 mg)	NR	Basiliximab	1 month	Excluded age>65, retransplants
Bechstein et al. 2013 ⁶⁷	Minimization of TAC	TAC (3–7 ng/mL) + SRL (8–15 ng/mL) + STER (prednisone 5 mg)	TAC (8–12 ng/mL) + SRL (5–10 ng/mL) + STER (prednisone 5 mg)	HP/LC-MS	Not used	Within 7 days	Excluded PRA>50% and "Patients at high risk"
Chadban et al. 2013 ⁴⁵	Minimization of CsA	CsA (C2 target 550–700 ng/mL) + EC-MPS (1,440 mg) + STER	CsA (C2 target 850–1,000 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	4 weeks	Excluded age>75, PRA>50%, retransplants
Cibrik et al. 2013 ⁶⁰	Minimization of CsA	CsA (25–50 ng/mL) + EVR (3–8 ng/mL OR 6–12 ng/mL) + STER	CsA (100–250 ng/mL) + MPA (1,440 mg) + STER	LC-MS	Basiliximab	24 hours	Excluded age>70, PRA>50%
Takahashi et al. 2013 ⁶¹	Minimization of CsA	CsA (25–50 ng/mL) + EVR (3–8 ng/mL) + STER (minimum 5 mg)	CsA (100–250 ng/mL) + MMF (2,000 mg) + STER (minimum 5 mg)	NR	Basiliximab	24 hours	Excluded age>65, PRA >50%, delayed graft function
Chan et al. 2012 ⁵⁶	Minimization of TAC	TAC (3–6 ng/mL) + EC-MPS (1,440 mg) + STER (prednisone 5 mg)	TAC (8–12 ng/mL) + EC-MPS (1,440 mg) + STER (prednisone 5 mg)	NR	Basiliximab	24 hours	Excluded age>70, PRA >20%, retransplants

Table E-1. Study design characteristics of minimization studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Kamar et al. 2012 ⁵⁷	Minimization of TAC	TAC (2–4.5 ng/mL) + EC-MPS (1,440 mg) + STER	TAC (5.5–10 ng/mL) + EC-MPS (720 mg) + STER	IA	NR	Minimum 1 year	Excluded age>75
Langer et al. 2012 ⁶⁸	Minimization of TAC	TAC (1.5–3 ng/mL) + EVR (3–8 ng/mL) + STER (prednisone 5 mg)	TAC (4–7 ng/mL) + EVR (3–8 ng/mL) + STER (prednisone 5 mg)	LC-MS	Basiliximab	3 months	Excluded PRA >50%, retransplants
Paoletti et al. 2012 ⁶³	Minimization of CsA	CsA (50–100 ng/mL) + EVR (3–8 ng/mL) + STER	CsA (125–250 ng/mL) + MMF (dose not reported) + STER	NR	Basiliximab	Immediate	Excluded age>70
Bertoni et al. 2011 ⁶⁴	Minimization of CsA	CsA (C2 target 250–300 ng/mL) + EVR (8–12 ng/mL) + STER	CsA (C2 target 500–700 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	Immediate	Excluded age>65, PRA >50%, retransplants
Holdaas et al. 2011 ²²	Minimization of CNI	CNI (CsA or TAC) at 70%–90% reduction from baseline + EVR (3–8 ng/mL) + prior therapy (could include MPA, AZA, and/or STER)	CsA (C2 target ≥400 ng/mL) or TAC (≥4 ng/mL) + prior therapy (could include MPA, AZA, and/or STER)	NR	NR	Minimum 6 months	NR
Xu et al. 2011 ³⁹	Minimization of CNI	CNI (CsA 80–120 ng/mL or TAC 3–6 ng/mL) + MMF (1,500 mg) + STER (prednisone 5 mg)	CNI (CsA 120–180 ng/mL or TAC 6–10 ng/mL) + MMF (1,500 mg) + STER (prednisone 5 mg)	IA	NR	Immediate	Excluded retransplants
Etienne et al. 2010 ⁴⁶	Minimization of CsA	CsA (2.0–2.6 mg h/L) + MMF (2,000 mg)	CsA (3.5–4.8 mg h/L) + MMF (2,000 mg)	LC-MS	rATG (72%) Interleukin-2 receptor antagonists (28%)	1 year	Excluded age>75, PRA>80%
Fangmann et al. 2010 ⁴⁷	Minimization of CsA	CsA (50–75 ng/mL) + MMF (2,000 mg) + STER (minimum 5mg)	CsA (100–150 ng/mL) + MMF (2,000) + STER (minimum 5mg)	NR	Daclizumab in intervention group	Shortly after transplant	Excluded PRA >20%, retransplants
Gaston et al. 2009 ⁴⁰	Minimization of CNI	CNI (CsA 95–145 ng/mL or TAC 3–5 ng/mL) + MMF (≥1.3 µg/mL for patients on CsA or ≥1.9 µg/mL for patients on TAC) + STER	CNI (CsA 190–220 ng/mL or TAC 6–8 ng/mL) + either MMF (≥1.3 µg/mL for patients on CsA or ≥1.9 µg/mL for patients on TAC) or MMF fixed dose (mean 1,834 mg for patients on CsA or mean 1,663 mg for patients on TAC) + STER (both comparison groups)	NR	"administered according to center practice"	Within 24 hours	NR

Table E-1. Study design characteristics of minimization studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Salvadori et al. 2009 ⁶⁵	Minimization of CsA	CsA (C2 target 150–300 ng/mL) + EVR (8–12 ng/mL) + STER (prednisone 5 mg)	CsA (C2 target 350–450 ng/mL) + EVR (3–8 ng/mL) + STER (prednisone 5 mg)	NR	Basiliximab	Within 24 hours	Excluded age>65, PRA >50%
Spagnetti et al. 2009 ⁴¹	Minimization of CNI and switch from CsA to TAC	TAC (5–8 ng/mL) + MMF (1,000 mg) + STER	CsA (C2 target 150–400 ng/mL) + EVR (3–8 ng/mL) + STER	NR	Basiliximab	24 hours	NR
Bolin et al. 2008 ⁵⁸	Minimization of TAC	TAC (3.0–5.9 ng/mL) + continuation of previous adjunct therapy (AZA, MMF, SLR, and/or STER)	TAC (6.0–8.9 ng/mL) or CsA (50–250 ng/mL) + continuation of previous adjunct therapy (AZA, MMF, SLR, and STER)	NR	NR	Minimum 6 months	NR
Chan et al. 2008 ⁶⁹	Minimization of TAC	TAC (3–6 ng/mL) + EVR (3–12ng/mL) + STER (\geq 5 mg)	TAC (7–10 ng/mL) + EVR (3–12ng/mL) + STER (\geq 5 mg)	LC-MS	Basiliximab	Within 24 hours	Excluded age>65, PRA >50%
Budde et al. 2007 ⁴⁸	Minimization of CsA	CsA (C2 target 550–700 ng/mL) + EC-MPS (1,440 mg) + STER	CsA (C2 target 850–1,000 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	2 months	Excluded age>75, PRA >50%
Cibrik et al. 2007 ⁴⁹	Minimization of CsA	CsA (C2 target 600–800 ng/mL) + EC-MPS (1,440 mg; high risk patients could receive up to 2,160 mg) + STER	CsA (C2 target 800–1,000 ng/mL) + EC-MPS (1,440 mg; high risk patients could receive up to 2,160 mg) + STER	HPLC or IA	Basiliximab	2 months	Excluded age>70, PRA >20%
Ekberg et al. 2007a ²⁴	Minimization of CsA	CsA (50–100 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	CsA (100–200 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	NR	Daclizumab in intervention group	Immediate	Excluded PRA >20%, retransplants
Ekberg et al. 2007b ⁴	Minimization of CNI	CsA (50–100 ng/mL) or TAC (3–7 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	CsA (100–200 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	IA	Daclizumab in intervention group	Immediate	Excluded age>75, PRA >20%
Ghafari et al. 2007 ⁵⁰	Minimization of CsA	CsA (125–175 ng/mL) + MMF (30 mg/kg) + STER (methylprednisolone 0.10 mg)	CsA (150 ng/mL) + MMF (30 mg/kg) + STER (methylprednisolone 0.10 mg)	IA	None used	Immediate	Excluded retransplants
Hernandez et al. 2007 ⁴²	Minimization of CNI	CsA (125–175 ng/mL) or TAC (7–10 ng/mL) + MMF (2,000 mg) + STER (prednisone 5–10 mg)	CsA (150–200 ng/mL) + AZA (1.5 mg/kg/day) + STER (prednisone 5–10 mg)	IA	Basiliximab (intervention group) and ATG (control group)	Within 24 to 48 hours	Excluded PRA >30%

Table E-1. Study design characteristics of minimization studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Frimat et al. 2006 ⁵¹ Frimat et al. 2010 ⁵²	Minimization of CsA	CsA (reduced by 50% from previous regimen) + MMF (2,000 mg) + STER	CsA with or without AZA + STER	NR	NR	Minimum 1 year	All patients had chronic allograft dysfunction; excluded age>65
Tang et al. 2006 ⁴³	Minimization of CsA	CsA (80–100 ng/mL) + “other medications according to centre protocol” including MMF, AZA	Conversion from previous CsA regimen to TAC (6–8 ng/mL)	IA	NR	Minimum 12 months	All patients had chronic allograft dysfunction; excluded age>65
Vathsala et al. 2005 ³⁸	Minimization of CsA	CsA (90–110 ng/mL) + Alemtuzumab (20 mg twice)	CsA (180–225 ng/mL) + AZA (1 mg/kg/day) + STER	NR	Alemtuzumab in intervention group	Immediate	Excluded age>65, PRA >85%
Lo et al. 2004 ⁷⁰	Minimization of TAC	TAC (5–10 ng/mL) + SRL (10–15 ng/mL) + STER (prednisone 5 mg)	TAC (10–15 ng/mL) + SRL (5–10 ng/mL) + STER (prednisone 5 mg)	IA (TAC) HPLC (SRL)	rATG	Within 2 days	NR
Nashan et al. 2004 ⁶⁶	Minimization of CsA	CsA (50–100 ng/mL) + EVR (3 mg) + STER (prednisone ≥ 5 mg)	CsA (125–250 ng/mL) + EVR (3 mg) + STER (prednisone ≥ 5 mg)	NR	Basiliximab	Within 24 hours	Excluded age>65, PRA >80%
Stoves et al. 2004 ⁵³	Minimization of CsA	CsA (75–100 ng/mL) + MMF (2,000 mg)	CsA (“per unit protocol”; data not reported) + AZA	NR	NR	Minimum 6 months	All patients had chronic allograft dysfunction
Pascual et al. 2003 ⁵⁴	Minimization of CsA	CsA (50–150 ng/mL) + MMF (1,500–2,000 mg) + STER (prednisone 7.5–10 mg)	CsA (100–300 ng/mL) + MMF (1,500–2,000 mg) + STER (prednisone 7.5–10 mg)	IA	NR	Minimum 12 months	NR
de Sevaux et al. 2001 ⁵⁵	Minimization of CsA	CsA (150 ng/mL) + MMF (2,000 mg) + STER (prednisone 0.1 mg/kg)	CsA (150 ng/mL) + MMF (2,000 mg) + STER (prednisone 0.1 mg/kg)	IA	NR	48 hours	NR

AR=acute rejection; AZA=azathioprine; ATG/rATG=antithymocyte globulin; CNI=calcineurin inhibitors; CsA=cyclosporine; EC-MPS=enteric-coated mycophenolate sodium; EVR=everolimus; h/L=hectoliter; HPLC=high performance liquid chromatography; IA=immunoassay; LC=liquid chromatography; mg=milligram; mg/kg=milligram per kilogram; MMF=mycophenolate mofetil group; MPA=medroxyprogesterone acetate; MPS=mycophenolate sodium; MS=mass spectrometry; ng/mL=nanogram per milliliter; NR=not reported; PRA=panel reactive antibody; SRL=sirolimus; STER=steroid ;TAC=tacrolimus; µg/mL=micrograms per milliliter

Table E-2. Study population characteristics of minimization studies

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Cai et al. 2014 ⁴⁴	Minimization of CsA	China	90	90	Living related Living unrelated	34 vs.33	73%	NR	12% vs. 18%
Chadban et al. 2014 ²³	Minimization of CsA	Asia Australia New Zealand	30	47	Deceased: 52 Living related: 51 Living unrelated: 23	43 vs. 46	71%	51%	NR
Muhlbacher et al. 2014 ⁵⁹	Minimization of CsA	Europe	178	179	Deceased: 314 Living related: 39 Living unrelated: 2	47 vs. 46	68%	94%	6% vs. 9%
Oh et al. 2014 ⁶²	Minimization of CsA	Korea	67	72	Deceased: 25 Living related: 79 Living unrelated: 35	42 vs. 47	60%	NR	NR
Bechstein et al. 2013 ⁶⁷	Minimization of TAC	Europe	63	65	Deceased	48 vs.45	65%	100%	30% vs. 31%
Chadban et al. 2013 ⁴⁵	Minimization of CsA	Australia	42	33	Deceased: 41 Living : 34	44 vs. 48	63%	85%	NR
Cibrik et al. 2013 ⁶⁰	Minimization of CsA	Worldwide	556	277	Deceased: 385 Living related: 311 Living unrelated: 135	46 vs. 45 vs. 47	67%	68%	NR
Takahashi et al. 2013 ⁶¹	Minimization of CsA	Japan	61	61	Deceased: 2 Living related: 79 Living unrelated: 41	42 vs. 39	68%	NR	NR
Chan et al. 2012 ⁵⁶	Minimization of TAC	USA	151	141	Deceased, living related and living unrelated	48 vs. 45	69%	86%	24% overall
Kamar et al. 2012 ⁵⁷	Minimization of TAC	France	45	47	Deceased: 88 Live unrelated: 4	51 vs. 54	66%	96%	NR
Langer et al. 2012 ⁶⁸	Minimization of TAC	Worldwide	107	117	Deceased: 160 Living related: 39 Living unrelated: 25	45 vs. 47	57%	83%	NR
Paoletti et al. 2012 ⁶³	Minimization of CsA	Italy	10	20	Deceased	47 vs. 51	70%	NR	NR
Bertoni et al. 2011 ⁶⁴	Minimization of CsA	Italy	56	50	NR	46 vs. 50	NR	NR	23% vs. 41%
Holdaas et al. 2011 ²²	Minimization of CNI	Worldwide	144	123	Deceased: 158 Living: 107 Missing: 4	50 vs. 48	65%	72%	NR
Xu et al. 2011 ³⁹	Minimization of CNI	China	20	18	Living related	29 vs. 32	82%	NR	NR

Table E-2. Study population characteristics of minimization studies (continued)

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Etienne et al. 2010 ⁴⁶	Minimization of CsA	France	106	102	Deceased	52 vs. 51	69%	98%	3% vs. 4%
Fangmann et al. 2010 ⁴⁷	Minimization of CsA	Europe	75	73	Deceased	52 vs. 54	62%	NR	27% vs. 27%
Gaston et al. 2009 ⁴⁰	Minimization of CNI	USA	243	477	Deceased: 361 Living related: 206 Living unrelated: 148	48 vs. 49 (MMF concentration controlled) vs. 50 (MMF fixed dose)	67%	69%	NR
Salvadori et al. 2009 ⁶⁵	Minimization of CsA	Italy	143	142	Deceased: 278 Living: 7	45 vs. 46	40%	64%	23% vs. 31%
Spagnoli et al. 2009 ⁴¹	Minimization of CNI and switch from CsA to TAC	Italy	30	30	Deceased	NR	NR	100%	NR
Bolin et al. 2008 ⁵⁸	Minimization of TAC	USA	100	223	Deceased: 168 Live: 155	50 vs. 48 (TAC) vs. 51 (CsA)	66%	73%	NR
Chan et al. 2008 ⁶⁹	Minimization of TAC	USA	49	43	Deceased: 31 Living related: 36 Living unrelated: 25	47 vs. 47	62%	66%	DGF Intervention: 4 (8.2%) of Control: 4 (9.3%)
Budde et al. 2007 ⁴⁸	Minimization of CsA	Germany	44	45	Deceased: 64 Living: 35	45 vs. 49	69%	93%	NR
Cibrik et al. 2007 ⁴⁹	Minimization of CsA	USA	75	66	Deceased: 73 Living related: 62 Living unrelated: 29	49 vs. 47	61%	61%	NR
Ekberg et al. 2007a ³⁴	Minimization of CsA	Worldwide	183	173	Deceased: 277 Living related: 47 Living unrelated: 32	48 vs. 49	65%	84%	20% vs. 22%
Ekberg et al. 2007b ³	Minimization of CNI	Worldwide	CsA: 399 TAC: 401	390	Deceased: 764 Living related: 345 Living unrelated: 79	47 (CsA) vs. 45 (TAC) vs. 46	65%	93%	NR
Ghafari et al. 2007 ⁵⁰	Minimization of CsA	Iran	42	48	Living	49 vs. 47	47%	NR	NR
Hernandez et al. 2007 ⁴²	Minimization of CNI	Spain	160	80	Deceased	48 vs. 47 vs. 47	64%	NR	32% vs. 40% vs. 27%
Frimat et al. 2006 ⁵¹ Frimat et al. 2010 ⁵²	Minimization of CsA	France	70	31	Deceased Living	44 vs. 45	81%	NR	NR

Table E-2. Study population characteristics of minimization studies (continued)

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Tang et al. 2006 ⁴³	Minimization	Hong Kong	18	16	Deceased: 26 Living related: 8	45 vs. 48.5	62%	NR	NR
Vathsala et al. 2005 ³⁸	Minimization of CsA	Asia	20	10	Deceased: 14 Living related: 14 Living unrelated: 2	Median: 38 vs. 41	50%	NR	20% vs. 10%
Lo et al. 2004 ⁷⁰	Minimization of TAC	USA	23	16	Deceased	Median: 49 vs. 46	59%	21%	57% vs. 63%
Nashan et al. 2004 ⁶⁶	Minimization of CsA	USA Europe	58	53	Deceased: 89 Living related: 17 Living unrelated: 5	44 vs. 46	61%	75%	NR
Stoves et al. 2004 ⁵³	Minimization of CsA	United Kingdom	13	16	NR	NR	NR	NR	NR
Pascual et al. 2003 ⁵⁴	Minimization of CsA	USA	32	32	Deceased: 37 Living related: 18 Living unrelated: 9	47 vs. 45	75%	64%	0 vs. 3%
de Sevaux et al. 2001 ⁵⁵	Minimization of CsA	Netherlands	152	161	Deceased: 233 Living: 80	49 vs. 48	62%	NR	NR

CNI=calcineurin inhibitors; CsA=cyclosporine; DGF=delayed graft function; MMF=mycophenolate mofetil group; NR=not reported; TAC=tacrolimus

Table E-3. Clinical outcomes of minimization studies

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, μmol/L	Regimen Changed	Other
Cai et al. 2014 ⁴⁴	1 year	Mean CsA C2 level: 363±149 ng/mL vs. 739±174 ng/mL	12/90 vs. 15/90 (BPAR, graft loss, patient death, lost to follow up)	10 vs. 12	1 vs. 2	1 vs. 1	63±19 vs. 59±15 (Cockcroft-Gault)	137±176 vs. 142±118	19 vs. 20	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Chadban et al. 2014 ²³	1 year		11 vs. 8	5 vs. 6 Banff (year not reported): Grade 1A: 5 vs. 3 Grade 1B: 0 vs. 4 Grade 2A: 0 vs. 0 Grade 2B: 0 vs. 1 Grade 3: 0 vs. 1 Unspecified: 0 vs. 2	0 vs. 2	0 vs. 1	NR	NR	NR	NR
Muhlbacher et al. 2014 ⁵⁹	1 year	Mean CsA level lower in intervention group, specific data NR	NR	20/178 vs. 29/179, p=NS Banff 97: Grade 1A: 9 vs. 14; Grade 1B: 3 vs. 9; Grade 2A: 4 vs. 3; Grade 2B: 3 vs. 2; Grade 3: 1 vs. 1	6 months: 0 vs. 2 12 months: 1 vs. 2	6 months: 0 12 months: 0 vs. 3	6 months: 55.9±1.67 vs. 51.0±1.67, p=0.04 12 months: 57.8±1.78 vs. 49.5±2.46, p<0.01 (Nankivell)	6 months: 1.79 vs. 2.00, p=0.03 12 months: 1.75 vs. 1.97, p<0.01	NR	NR
Oh et al. 2014 ⁶²	1 year	Mean trough level: 54.1 ng/mL vs. 120.4 ng/mL Intervention group mean above target range, but lower than control group (p<0.01)	NR	5/67 vs. 8/72	0 vs. 1	0	5 months: 66.7±17.5 vs. 59.5±16.4, p=0.02 12 months: 69.5±17.2 vs. 61.2±17.9, p=0.01 (MDRD)	NR	NR	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Bechstein et al. 2013 ⁶⁷	6 months	Mean TAC levels achieved throughout study	NR	11/63 vs. 5/65 Banff 97: Grade 1A: 4 vs. 4; Grade 2A: 5 vs. 0; Grade 2B: 2 vs. 1	4 vs. 1	3 vs. 2	63.8±17.3 vs. 52.7±18.9, p=0.005 (Nankivell)	136 vs. 153, p=NS	NR	NR
Chadban et al. 2013 ⁴⁵	1 year	Mean C2 target achieved in both groups: 640±216 vs. 876±250	6 months: 15/42 vs. 10/33 12 months: 18 vs. 12 (BPAR, graft loss, patient death)	6 months: 12 vs. 8 12 months: 15 vs. 10	6 month: 3 vs. 1 12 months: 3 vs. 1	6 months: 0 vs. 1 12 months: 0 vs. 1	6 months: 63.2±24.3 vs. 60.2±17.6 12 months: 60.7±20.1 vs. 63.3±17.5 (Cockcroft-Gault)	NR	8 vs. 13	NR
Cibrik et al. 2013 ⁶⁰	2 years	Mean trough CsA level: 42.7 ng/mL (low EVR) vs. 47.9 ng/mL (high EVR) vs. 120.5 ng/mL (standard dose EVR and CsA)	91/277 (low EVR) vs. 75/279 (high EVR) vs. 76/277 (standard) (BPAR, graft loss, patient death, lost to follow-up)	55 (low EVR) vs. 42 (high EVR) vs. 53 (standard) Banff 03: Grade 1A: 25 vs. 20 vs. 27 Grade 1B: 13 vs. 10 vs. 8 Grade 2A: 10 vs. 9 vs. 17 Grade 2B: 2 vs. 4 vs. 3 Grade 3: 2 vs. 0 vs. 2	16 (low EVR) vs. 17 (high EVR) vs. 11 (standard)	9 (low EVR) vs. 10 (high EVR) vs. 8 (standard)	Median: 54.0 vs. 55.4 vs. 51.4 (MDRD) Median: 64.7 vs. 64.4 vs. 62.1 (Nankivell) Median: 67.4 vs. 66.4 vs. 65.0 (Cockcroft-Gault)	NR	80 vs. 85 vs. 57, p<0.05 compared with both groups	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Takahashi et al. 2013 ⁶¹	1 year	Median CsA trough level: 63.0 ng/mL vs. 130.5 ng/mL, but “a higher proportion of EVR patients were above the cyclosporine target range versus the MMF group”	7/61 vs. 7/61 (BPAR, graft loss, patient death, lost to follow-up)	3 vs. 5 Banff 03: Grade 1A: 2 vs. 2 Grade 1B: 0 vs. 1 Grade 2A: 1 vs. 2	0	0	62.09±18.99 vs. 56.34±15.23, p=NS (MDRD)	NR	9 vs. 8	NR
Chan et al. 2012 ⁵⁶	6 months	24%–52% of intervention group exceeded trough target; 31%–53% of control group below trough target	22/151 vs. 16/141 (BPAR, graft loss, patient death)	16 vs. 14 Banff 97: Grade 1A: 6 vs. 6 Grade 1B: 2 vs. 3 Grade 2A: 5 vs. 3 Grade 2B: 2 vs. 2 Missing: 1 vs. 0	6 vs. 2	1 vs. 2	63.6±4.8 vs. 61.0±4.9, p=NS (Nankivell) 62.1 vs. 59.5, p=NS (Cockcroft-Gault)	144 vs. 135, p=NS	4 vs. 4	NR
Kamar et al. 2012 ⁵⁷	6 months	Mean TAC levels for intervention group not reached until 3 months into study	NR	0	0	0	6 months: 49.1±11.1 vs. 44.7±11.5, p=0.07 Change from baseline: 2.48±0.95 vs. -0.48±0.93, p=0.03 (aMDRD)	6 months: 137±33 vs. 147±39, p=0.30 Change from baseline: 6.2±2.8 vs. 4.3±2.8, p=0.01	2 vs. 1	NR
Langer et al. 2012 ⁶⁸	1 year	56% of intervention group exceeded trough target; 30% of control group not in target range	5/107 vs. 4/117 (BPAR, graft loss, patient death, lost to follow-up) Treatment/Efficacy failure: 29 vs. 14 [12months]	2 vs. 1	1 vs. 1	2 vs. 1	57.1±19.5 vs. 51.7±20 (MDRD) 67.1 ±23.0 vs. 61.1±19.7 (Cockcroft-Gault)	1.44±0.51 mg/dL vs. 1.60±0.71 mg/dL	19 vs. 12	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, $\mu\text{mol/L}$	Regimen Changed	Other
Paoletti et al. 2012 ⁶³	1 year	NR	NR	1/10 vs. 2/20	0	0	NR	Change from baseline: -0.04 \pm 0.4 mg/dL vs. -0.08 \pm 0.3 mg/dL, p=NS	0 vs. 1	NR
Bertoni et al. 2011 ⁶⁴	1 year	NR	NR	11/56 vs. 9/50	3 vs. 6	NR	81.64 \pm 32.67 vs. 62.62 \pm 22.81, p<0.01 (Cockcroft-Gault)	NR	5 vs. 3	Mean length of hospital stay: 24.77 \pm 11.13 days vs. 24.57 \pm 12.20 days
Holdaas et al. 2011 ²²	2 years	CsA dose reduced by mean 78%, TAC by mean 66%	17/144 vs. 11/123	8 vs. 3 Grade 1A: 4 vs. 1 Grade 2A: 2 vs. 0 Grade 3: 1 vs. 0 Missing: 1 vs. 2	8 vs. 6	3 vs. 0	52.0 \pm 18.7 vs. 53.6 \pm 21.1 (Cockcroft-Gault)	171 \pm 102 vs. 168 \pm 81	25 vs. 5	NR
Xu et al. 2011 ³⁹	1 year	NR	NR	4/20 vs. 3/18	0 vs. 1	0 vs. 1	59.4 \pm 27.4 vs. 58.9 \pm 29.8	No significant difference	NR	NR
Etienne et al. 2010 ⁴⁶	2 years	Intervention group mean trough levels were significantly lower than control group, p<0.01	19/106 vs. 37/101, p<0.01 (BPAR, graft loss, CsA toxicity, >15% increase in mean Scr)	6 vs. 3 Bannf 97: Grade 1: 0 vs. 2 Grade 2: 5 vs. 1 Grade 3: 1 vs. 0	0 vs. 1	NR	Change from baseline: 0.57 \pm 8.80 vs. -4.27 \pm 8.06	Change from baseline: 0 \pm 0.34 mg/dL vs. 0.18 \pm 0.82 mg/dL	NR	CAN: 2 vs. 2
Fangmann et al. 2010 ⁴⁷	1 year	NR	NR	2/75 vs. 19/73, p<0.05	5 vs. 15	2 vs. 5	34.1 \pm 17.4 vs. 29.4 \pm 16.5, p<0.05 (Cockcroft-Gault)	NR	4 vs. 8	NR
Gaston et al. 2009 ⁴⁰	1 year	Mean target for intervention group not achieved, but was statistically significantly lower than both comparison groups	55/243 vs. 137/477 (BPAR, graft loss, patient death, lost to follow-up, withdrawn consent)	15 vs. 46	5 vs. 8	4 vs. 8	Change from baseline: 12.3% vs. 5.4% vs. 8.2% (Nankivell)	NR	18 vs. 68, p<0.05	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Salvadori et al. 2009 ⁶⁵	6 months	Mean CsA levels exceeded target range in intervention group	NR	16/142 vs. 20/143	3 vs. 14, p<0.01	2 vs. 2	6 months: 60.0±16.4 vs. 62.3±15.6 12 months: 63.8±18.3 vs. 64.8±17.7 (Nankivell) 6 months: 57.8±19.3 vs. 59.9±18.6 12 months: 61.3±22.0 vs. 62.5±20.7 (Cockcroft-Gault)	6 months: 1.63 vs. 1.56 mg/dL 12 months: 1.55 vs. 1.51 mg/dL	33 vs. 25	NR
Spagnolletti et al. 2009 ⁴¹	6 months	NR	NR	NR	1/30 vs. 2/30	0	NR	NR	NR	NR
Bolin et al. 2008 ⁵⁸	1 year	24% of intervention group exceeded TAC trough target; 34% of control group lower than TAC trough target	NR	2/100 vs. 2/112 (standard TAC) vs. 3/111 (standard CsA) Grade 1A: 0 vs. 1 vs. 1 Grade 1B: 1 vs. 1 vs. 1 Grade 2A: 1 vs. 0 vs. 1	0 vs. 1	0	Median change from baseline: 1.65 vs. -0.60 (standard TAC) vs. -0.80 (standard CsA) (Cockcroft-Gault)	Median change from baseline: -0.10 mg/L vs. 0	1 vs. 8 vs. 7	NR
Chan et al. 2008 ⁶⁹	6 months	Intervention: Mean TAC trough levels higher than target; at 6 months intervention TAC level = 7.1, control TAC level = 7.2	7/49 vs. 7/43	7 vs. 6 Banff 97: Grade 1: 5 vs. 4 Grade 2A: 1 vs. 1 Unknown: 1 vs. 1	0 vs. 1	0	75.3±16.6 vs. 72.5±15.2 (Nankivell) 82.8±26.8 vs. 77.2±21.8 (Cockcroft-Gault)	112±31 mg/dL vs. 127±50 mg/dL	5 vs. 4	CAN: 0 vs. 2

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Budde et al. 2007 ⁴⁸	1 year	Intervention group achieved target (mean: 688 ± 238 ng/mL) at 12 months Control group below target (mean: 781 ± 215 ng/mL) at 12 months Intervention group 10-15% below control group	6 months: 7/44 vs. 8/45 1 year: 8 vs. 9 (BPAR, graft loss, patient death)	6 months: 6 vs. 8 1 year: 7 vs. 8 Banff 97: Grade 1: 4 vs. 7 Grade 2: 3 vs. 2 (1 patient had two episodes)	0	6 months: 2 vs. 0 1 year: 3 vs. 1	6 months: 61.5 ± 3.7 vs. 55.3 ± 3.2 1 year: 59.7 ± 4.1 vs. 56.6 ± 3.2 (Cockcroft-Gault)	6 months: 145 vs. 160 1 year: 1 62 vs. 163	5 vs. 3	NR
Cibrik et al. 2007 ⁴⁹	1 year	From months 3-12, 18%-37% of intervention group achieved target C2, 26%-40% of control group achieved target C2	13/75 vs. 16/66 (BPAR, graft loss, patient death)	11 vs. 16 Banff 97: Grade 1A: 8 vs. 10 Grade 1B: 2 vs. 3 Grade 2A: 0 vs. 1 Grade 2B: 1 vs. 2	1 vs. 1	1 vs. 0	79.2 vs. 71.0, p<0.05 Change from baseline: 9.6 vs. 6.6 (Cockcroft-Gault)	132 vs. 141	NR	NR
Ekberg et al. 2007a ²⁴	1 year	9% of intervention group patients exceeded target level some time during the study	NR	46/183 vs. 48/173	6 vs. 9	4 vs. 5	50.9 \pm 6.4 vs. 48.6 \pm 6.9 (Cockcroft-Gault)	1.5 mg/dL vs. 1.6 mg/dL	NR	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Ekberg et al. 2007 ^b ⁴	1 year	Mean trough levels were within the target levels for all groups	Low dose CsA: 81 Low dose TAC: 49 Standard dose CsA: 89 (Graft loss, death, use of additional immuno-suppression, discontinuation of study medication for >14 consecutive or 30 cumulative days)	6 months: Low dose CsA: 87 Low dose TAC: 45 Standard dose CsA: 94 1 year: Low dose CsA: 109 Low dose TAC: 62 Standard dose CsA: 117	Low dose CsA: 23 Low dose TAC: 14 Standard dose CsA: 32	Low dose CsA: 7 Low dose TAC: 11 Standard dose CsA: 13	Low dose CsA: 59.4±25.1 (Cockcroft-Gault) 50.2±23.1 (MDRD) Low dose TAC: 65.4±27.0 (Cockcroft-Gault) 54.3±23.9 (MDRD) Standard dose CsA: 57.1±25.1 (Cockcroft-Gault) 46.2±23.1 (MDRD)	NR	NR	NR
Ghafari et al. 2007 ⁵⁰	2 years	NR	NR	20/42 vs. 25/48	8 vs. 10	1 vs. 1	NR	No significant difference (data not reported)	3 vs. 3	No difference in length of hospital stay or readmissions

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Hernandez et al. 2007 ⁴²	2 years	Low dose CsA trough level: 133±61 Low dose TAC trough level: 7.5±2 Standard CsA trough level: 126±46	NR	Low dose CsA: 11 Banff 97: Grade 1: 6 Grade 2: 4 Grade 3: 1 Low dose TAC: 13 Grade 1: 7 Grade 2: 4 Grade 3: 2 Standard CsA: 12 Grade 1: 9 Grade 2: 2 Grade 3: 1	Low dose CsA: 4 vs. 4 Low dose TAC: 7 vs. 4	Low dose CsA: 4 vs. 3 Low dose TAC: 8 vs. 3	Low dose CsA: 66±20 (Cockcroft-Gault) 56±21 (Jelliffe 2) 59±24 (MDRD) Low dose TAC: 70±27 (Cockcroft-Gault) 59±20 (Jelliffe 2) 62±22 (MDRD) Standard dose CsA: 58±14 (Cockcroft-Gault) 51±17 (Jelliffe 2) 52±18 (MDRD)	NR	Low dose CsA: 10 Low dose TAC: 6 Standard dose CsA: 10	CAN: 1 in low dose CsA group
Frimat et al. 2006 ⁵¹ Frimat et al. 2010 ⁵²	5 years	Intervention group trough levels were lower than control group at study completion: 71 vs. 117 ng/mL	NR	2 years: 0 5 years: 0 vs. 1	2 years: 1/70 vs. 1/31 5 years: 2 vs. 2	2 years: 0 5 years: 0 vs. 1	2 years: 56.2±16.6 vs. 45.1±16.4 (Cockcroft-Gault) 5 years: 51.8±20.2 vs. 41.3±18.9	NR	NR	NR
Tang et al. 2006 ⁴³	15 months	NR	NR	0/18 vs. 2/16	0 vs. 2	NR	39.8±20.2 vs. 32.9±11.1	NR	NR	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, $\mu\text{mol/L}$	Regimen Changed	Other
Vathsala et al. 2005 ³⁸	6 months	Median CsA trough level: 119 vs. 172 ng/mL	NR	5/20 vs. 2/10 Banff 97: Border line: 2 vs. 1 Grade 1: 2 vs. 1 Grade 2A: 1 vs. 0	3 vs. 0	1 vs. 0	No significant difference (data not reported)	No significant difference (data not reported)	5 vs. 1	NR
Lo et al. 2004 ⁷⁰	6 months	Mean TAC 12 hour trough: 4.4 \pm 1.2 vs. 15.8 \pm 9.3	4/23 vs. 1/23 (BPAR, graft loss, patient death)	1/23 vs. 1/16	4/23 vs. 1/16	0/23 vs. 1/16	NR	1.6 \pm 0.9 mg/dL vs. 1.9 \pm 0.7 mg/dL, p=NS	6 vs. 9	Median hospital stay: 6 days (range 4–27) vs. 7 days (range 4–15) All-cause hospital re-admission: 44% vs. 56%
Nashan et al. 2004 ⁶⁶	3 years	Over 3 years, mean daily CsA dose significantly lower in intervention group (3.2 mg/kg vs. 2.0 mg/kg) Over first 6 months, CsA trough levels were 35% lower in intervention than control group	6 months: 2/53 vs. 8/58, p<0.05 1 year: 5 vs. 15, p<0.05 3 years: 10 vs. 19, p<0.05 (BPAR, graft loss, patient death, lost to follow-up)	6 months: 2 vs. 8 1 year: 4 vs. 9 3 years: 7 vs. 10	6 months: 1 vs. 1 1 year : 0 vs. 2 3 years: 1 vs. 3 3 years: 2 vs. 7	6 months: 0 1 year: 2 vs. 5	6 months: 59.7 \pm 11.7 vs. 51.1 \pm 15.0, p<0.01 1 year: 60.9 \pm 11.3 vs. 53.5 \pm 12.1, p<0.01 3 years: 56.6 \pm 20.0 vs. 51.7 \pm 13.1, p=NS (Nankivell)	NR	19 vs. 29, p<0.05	CAN: 1 year: 0 vs. 3 3 years: 7 vs. 11
Stoves et al. 2004 ⁵³	6 months	Median CsA trough level: 99 ng/mL vs. 163 ng/mL Mean dose reduction from baseline: 24%	6 (3-patient death, 3-lost to follow-up)	0	0	3 (during 9 months)	Median change over baseline: 2.5 vs. -0.7, p=0.05	NR	NR	NR

Table E-3. Clinical outcomes of minimization studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (method)	Mean Serum Creatinine, µmol/L	Regimen Changed	Other
Pascual et al. 2003 ⁵⁴	6 months	Mean CsA trough level at 6 months: 86 vs. 193 ng/mL	NR	0/32 vs. 0/32	0	0	64.6±20 vs. 61.0±19 Change from baseline: 7.1, p=0.01	1.33±0.26 vs. 1.40±0.25 Change from baseline: -0.06, p=0.06	NR	NR
de Sevaux et al. 2001 ⁵⁵	6 months	Median CsA trough level at 3 months: 154 vs. 248	NR	29/152 vs. 36/161, p=NS Banff 93: Grade 1: 16 vs. 20 Grade 2: 10 vs. 16 Grade 3: 3 vs. 0	8 vs. 14, p=NS	3 vs. 5	3 months: 66±36 vs. 59±32 6 months: 69±31 vs. 65±28	3 months: 142 vs. 151 6 months: 136 vs. 141	20 vs. 27	NR

aMDRD=abbreviated modification of diet in renal disease; BPAR=biopsy proven acute rejection; CAN=chronic allograft nephropathy; C2=2 hour post CsA dosage level; CsA=cyclosporine; EVR=everolimus; MDRD=modification of diet in renal disease; mg/dL=milligram per deciliter; MMF=mycophenolate mofetil group; ng/mL=nanogram per milliliter; NR=not reported; NS=not significant; SCr=serum creatinine; TAC=tacrolimus

Table E-4. Adverse events reported in minimization studies

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Cai et al. 2014 ⁴⁴	Minimization of CsA	NR	NR	Gastroenteritis: 5/90 vs. 4/90 UTI: 0 vs. 2	NR	NR	No difference	No difference for GI, anemia, leukopenia
Chadban et al. 2014 ²³	Minimization of CsA	12 vs. 13	0 vs. 1	CMV: 2 vs. 4 All infections: 18 vs. 34	NR	0 vs. 1	No difference between groups for cholesterol	No difference between groups for GI, anemia
Muhlbacher et al. 2014 ⁵⁹	Minimization of CsA	NR	1/178 (lymphoma-like reaction) vs. 2/179 (lymphoma-like reaction and renal carcinoma)	CMV: 13 vs. 14 Pneumonia: 10 vs. 16 Herpes: 10 vs. 9 Candida: 11 vs. 17 UTI: 47 vs. 45 Wound infection: 13 vs. 4	NR	NR	No difference for BP, cholesterol; control group had higher triglycerides	No difference for anemia, leukopenia, edema
Oh et al. 2014 ⁶²	Minimization of CsA	NR	NR	All infections: 36/67 vs. 60/72	NR	NR	No difference	No difference for GI, respiratory, vascular, nervous system
Bechstein et al. 2013 ⁶⁷	Minimization of TAC	9/63 vs. 8/65	1 (basal cell carcinoma) vs. 1 (post-transplant lymphoma)	CMV: 3/63 vs. 5/65 Candida: 2 vs. 4 Sepsis: 1 vs. 3 Pneumonia: 2 vs. 6 UTI: 8 vs. 3 Herpes: 1 vs. 1 Lymphocele: 6 vs. 7 Dehiscence: 3 vs. 1 Wound infection: 1 vs. 1	NR	NR	No difference	No difference for GI, anemia, leukopenia, edema
Chadban et al. 2013 ⁴⁵	Minimization of CsA		4 total (2 skin carcinoma, 1 post-transplant lymphoma, 1 Hodgkins; "no significant difference between groups")	30 vs. 26 (details not reported)	NR	NR	NR	No difference for GI

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Cibrik et al. 2013 ⁶⁰	Minimization of CsA	28/274 vs. 40/278 vs. 20/273	9 vs. 7 vs. 13	CMV infection: 4 vs. 1 vs. 25 CMV syndrome: 4 vs. 5 vs. 15 CMV disease: 2 vs. 3 vs. 8 BK virus: 2 vs. 4 vs. 13 UTI: 66 vs. 73 vs. 74 Upper respiratory tract: 54 vs. 49 vs. 63	8 vs. 21 vs. 11	NR	No difference for BP; total cholesterol and triglycerides lower in intervention group	No difference for GI; stomatitis higher in intervention group; leukopenia lower in intervention group
Takahashi et al. 2013 ⁶¹	Minimization of CsA	7 vs. 3	2 (thyroid cancer; b-cell lymphoma) vs. 0	CMV infection: 3 vs. 21 CMV test positive: 4 vs. 19 Nasopharyngitis: 21 vs. 26	NR	8 vs. 5	No difference	Nephrotoxicity: 13 vs. 6; No difference in GI, anemia, headache, stomatitis, hirsutism; edema higher in intervention group
Chan et al. 2012 ⁵⁶	Minimization of TAC	19/114 vs. 33/119	1/151 (renal cell carcinoma) vs. 2/141 (basal cell carcinoma, malignant melanoma)	Bacterial: 59 vs. 65 Viral: 33 vs. 27	NR	NR	NR	No difference for GI, anemia, edema
Kamar et al. 2012 ⁵⁷	Minimization of TAC	NR	NR	Any: 10 vs. 9 Bronchitis: 3 vs. 1 Pneumocystis jirovecii: 1 vs. 0 UTI: 1 vs. 2 Gastroenteritis: 1 vs. 4 Pyelonephritis: 0 vs. 1 Infected hygroma: 0 vs. 1	NR	NR	No difference for cholesterol, triglycerides	No difference for GI, anemia, edema
Langer et al. 2012 ⁶⁸	Minimization of TAC	14/109 vs. 18/119	NR	CMV: 2 vs. 3 BK: 5 vs. 1 UTI: 36 vs. 42 Bacterial: 39.4% vs. 35.3% Viral: 9.2% vs. 10.9% Fungal: 5.9% vs. 7.3%	NR	12 vs. 9	No difference for cholesterol	No difference for GI, anemia, edema, nervous system, hypokalemia, hyperkalemia
Paoletti et al. 2012 ⁶³	Minimization of CsA	2/10 vs. 2/20	NR	NR	NR	3 vs. 2	No difference for BP; cholesterol and triglycerides higher in intervention group	NR

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Bertoni et al. 2011 ⁶⁴	Minimization of CsA	NR	NR	CMV infection: 26% vs. 27% (specific data not reported) CMV disease rate: 8% vs. 10%	NR	519.7±77.31 mg/24 hours vs. 296.7±33.42 mg/24 hours, p=0.01	No difference for cholesterol; systolic BP lower in intervention group	NR
Holdaas et al. 2011 ²²	Minimization of CNI	7/144 vs. 4/123	11 vs. 7	Any infection: 89 vs. 75 UTI: 24 vs. 13 Upper respiratory tract: 16 vs. 16	NR	19 vs. 11	No difference for triglycerides or hypertension; cholesterol and hyperlipidemia higher in intervention group	Higher incidence of edema, pyrexia, rash in intervention group; no difference for GI, anemia
Xu et al. 2011 ³⁹	Minimization of CNI	NR	NR	Pulmonary: 1 vs. 3 (1 of these confirmed CMV)	NR	None	No difference for BP	Nephrotoxicity: 0/20 vs. 5/18 (p<0.05)
Etienne et al. 2010 ⁴⁶	Minimization of CsA	2 vs. 7	3 (1 skin cancer, 2 solid carcinoma) vs. 7 (5 skin cancer, 2 solid carcinoma)	Bacterial: 22/106 vs. 19/101 Viral: 4/106 vs. 9/101	NR	NR	No difference for cholesterol, triglycerides; BP lower in intervention group	Nephrotoxicity: 5/106 vs. 12/101 (p=0.08)
Fangmann et al. 2010 ⁴⁷	Minimization of CsA	NR	0	CMV: 19/75 vs. 15/73 Herpes: 6 vs. 11 Other viral: 9 vs. 4 Bacterial: 40 vs. 39 Fungal: 9 vs. 3	9 vs. 5; type unspecified	NR	No difference for BP and lipids	Neurological: 17 vs. 13 Metabolic: 22 vs. 14 GI: 13 vs. 10 Hematological: 14 vs. 19
Gaston et al. 2009 ⁴⁰	Minimization of CNI	2 (CsA) and 32 (TAC) vs. 3 (CsA) and 41 (TAC)	2 (CsA) and 3 (TAC) vs. 1 (CsA) and 12 (TAC)	All “opportunistic infections”: 22/238 vs. 55/471 CMV: 12/238 vs. 32/471 BK virus infection: 4/238 vs. 15/471 BK virus nephropathy: 0/238 vs. 8/471	NR	NR	No difference for hypertension, hyperlipidemia	No difference for GI, leukopenia
Salvadori et al. 2009 ⁶⁵	Minimization of CsA	7/142 vs. 3/143	2 vs. 2 (1 basal cell carcinoma, 1 epithelioma, 2 unspecified)	All infections: 88 vs. 96 CMV requiring hospitalization: 3 vs. 2 Pneumonia requiring hospitalization: 3 vs. 2	“Cardiac disorders”: 7 vs. 4	NR	No difference	No difference for GI, anemia, edema, vascular, metabolic

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Spagnetti et al. 2009 ⁴¹	Minimization of CNI and switch from CsA to TAC	1/30 vs. 4/30	NR	NR	NR	NR	No difference for BP; higher mean serum cholesterol and higher serum triglycerides for intervention group	NR
Bolin et al. 2008 ⁵⁸	Minimization of TAC	3/63 vs. 2/66 (standard TAC) vs. 3/66 (standard CsA)	9/100 vs. 6/112 (standard TAC) vs. 3/111 (standard CsA) (mainly basal and squamous cell carcinoma)	CMV: 0 vs. 3 (standard TAC) vs. 1 (standard CsA); 3 of these were donor derived All other infections: 16 vs. 30 (standard TAC) vs. 22 (standard CsA)	NR	NR	No difference for cholesterol, triglycerides	No difference for overall quality of life; lower GI distress for intervention group
Chan et al. 2008 ⁶⁹	Minimization of TAC	8/21 vs. 4/17	0 vs. 1 (adrenal neoplasm)	9/49 vs. 8/43 Pneumonia: 1 vs. 0 UTI: 6 vs. 7 Wound infection: 2 vs. 1	NR	0 vs. 1	Hypercholesterolemia: 5 (10.2%) vs. 4 (9.3%) Hypertriglyceridemia: 1 (2.0%) vs. 3 (7.0%) No difference for lipids, triglycerides	No difference for GI, edema, hematological Peripheral edema: 23 (47%) vs. 9 (20.9%)
Budde et al. 2007 ⁴⁸	Minimization of CsA	NR	NR	All infections (details NR): 30/44 vs. 35/45	NR	NR	No difference for BP	No difference for GI
Cibrik et al. 2007 ⁴⁹	Minimization of CsA	4 (groups not specified)	2 (groups not specified)	Candidiasis: 9/75 vs. 8/66 Oral candidiasis: 13 vs. 9 UTI: 9 vs. 21 Upper respiratory: 13 vs. 6	NR	NR	NR	No difference for GI, anemia, leukopenia, hirsutism
Ekberg et al. 2007a ²⁴	Minimization of CsA	NR	5 (including 1 post-transplant lymphoproliferative disorder) vs. 1	CMV: 20 vs. 24 Candida: 8 vs. 16 Herpes simplex: 13 vs. 11 Herpes zoster: 12 vs. 9 UTI: 8 vs. 7	NR	NR	No difference	No difference for lymphocele, hypertension

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Ekberg et al. 2007 ^b	Minimization of CNI	Low dose CsA: 17 Low dose TAC: 34 Standard dose CsA: 23	Low dose CsA: 4 (Kaposi's sarcoma, transitional-cell, renal-cell, basal-cell) Low dose TAC: 8 (3 basal-cell, 2 renal-cell, prostate, cerebral lymphoma, squamous cell) Standard dose CsA: 5 (2 basal-cell, squamous-cell, oral mucosa, Kaposi's sarcoma)	Low dose CsA: All "opportunistic infections" (per study designation): 93 CMV: 45 Candida: 19 Herpes simplex: 15 All other infections: 206 UTI: 97 Pneumonia: 5 Nasopharyngitis: 32 Low dose TAC: All "opportunistic infections" (per study designation): 80 CMV: 39 Candida: 12 Herpes simplex: 18 All other infections: 211 UTI: 95 Pneumonia: 13 Nasopharyngitis: 32 Standard dose CsA: All "opportunistic infections" (per study designation): 100 CMV: 55 Candida: 29 Herpes simplex: 21 All other infections: 208 UTI: 109 Pneumonia: 18 Nasopharyngitis: 22	Low dose CsA: 15 Low dose TAC: 13 Standard dose CsA: 15	Low dose CsA: 8 Low dose TAC: 20 Standard dose CsA: 9	No difference in hypercholesterolemia, hyperlipidemia, hypertriglyceridemia between low and standard dose CsA groups ; hypercholesterolemia and hyperlipidemia lower in low dose TAC group	No difference for anemia, leukopenia, edema, pyrexia, lymphocytosis, disorders of the nervous system, respiratory system, or vascular system; higher incidence of serious GI events in low dose TAC group
Ghafari et al. 2007 ⁵⁰	Minimization of CsA	No difference between groups (data not specified)	NR	No difference between groups (data not specified)	No difference between groups (data not specified)	NR	Lower hypertension, higher triglycerides in intervention group	Nephrotoxicity: 1 vs. 4; No difference for GI, hematological

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Hernandez et al. 2007 ⁴²	Minimization of CNI	Low dose CsA: 9/58 vs. 10/55 Low dose TAC: 15/55 vs. 10/55	Low dose CsA: 2 vs. 3 Low dose TAC: 2 vs. 3	Low dose CsA: CMV: 19 vs. 40 Pneumonia: 4 vs. 1 UTI: 25 vs. 23 Other viral: 8 vs. 5 Low dose TAC: CMV: 29 vs. 40 Pneumonia: 3 vs. 1 UTI: 28 vs. 23 Other viral: 5 vs. 5	NR	No difference	No difference for cholesterol, triglycerides	Nephrotoxicity: Low dose CsA: 12 vs. 18 Low dose TAC: 20 vs. 18 No difference for GI, anemia, leukopenia
Frimat et al. 2006 ⁵¹ Frimat et al. 2010 ⁵²	Minimization of CsA	NR	2 years: 3/70 vs. 2/33 5 years: 3 vs. 3	2 years: All infections: 33 vs. 10 Herpes simplex: 2 vs. 0 Herpes zoster: 3 vs. 1 Other herpes: 1 vs. 0 Bronchitis: 13 vs. 3 5 years: All infections: 6 vs. 2 Opportunistic infections: 0	2 years: NR 5 years: 4 vs. 1	2 years: 39% vs. 62%	NR	2 years: Higher incidence of GI, anemia in intervention group; no difference for leucopenia 5 years: no difference for GI, urinary system, kidney, thoracic, respiratory, mediastinal disorders
Tang et al. 2006 ⁴³	Minimization	NR	NR	UTI: 0/18 vs. 1/16 Gastroenteritis: 1 vs. 0 Herpes zoster: 0 vs. 1	NR	No difference	No difference	NR
Vathsala et al. 2005 ³⁸	Minimization of CsA	NR	0	CMV: 9/20 vs. 2/10 Herpes zoster: 1 vs. 0 Septicimia: 2 vs. 0 Pneumonia: 6 vs. 0 UTI: 9 vs. 6	NR	NR	No difference for BP	NR
Lo et al. 2004 ⁷⁰	Minimization of TAC	5/23 vs. 4/16	0	1 CMV in control group	1 idiopathic pulmonary hemorrhage in control group	NR	No difference for cholesterol, triglycerides	Nephrotoxicity: 7 cases in control group; No difference for leukopenia

Table E-4. Adverse events reported in minimization studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Nashan et al. 2004 ⁶⁶	Minimization of CsA	NR	3 vs. 2	CMV: 0 vs. 1 Herpes simplex: 0 vs. 3 Bacterial: 24 vs. 23 Fungal: 5 vs. 5 Pneumocystis carinii: 0 vs. 1	5 vs. 2 (myocardial infarction, angina pectoris, sudden death)	13 vs. 5	No difference	Nephrotoxicity: 2/58 vs. 6/53; No difference for GI
Stoves et al. 2004 ⁵³	Minimization of CNI	0	NR	UTI: 1 (control group)	NR	NR	No difference for BP, lipids	NR
Pascual et al. 2003 ⁵⁴	Minimization of CsA	NR	0	0	NR	NR	No difference	NR
de Sevaux et al. 2001 ⁵⁵	Minimization of CsA	6 vs. 6	0	CMV: 35 vs. 31 UTI: 38 vs. 34 Oral candidiasis: 12 vs. 14	NR	NR	No difference	Nephrotoxicity: 4/152 vs. 13/161, p=0.06

BK=BK polyomavirus; BP=blood pressure; CMV=cytomegalovirus; CNI=calcineurin inhibitors; CsA=cyclosporine; GI=gastrointestinal; NR=not reported; UTI=urinary tract infection; TAC=tacrolimus

Table E-5. Study design characteristics of conversion studies

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Bansal et al. 2013 ⁷²	Conversion from Control Regimen to SRL	SRL (8–15 ng/mL)	CsA (150–250 ng/mL) or TAC (6–8 ng/mL) + MMF + STER (prednisone 5 mg)	HPLC	NR	3 months	Only live donors included
Chhabra et al. 2013 ⁷⁷	Conversion from TAC to SRL	SRL (5–8 ng/mL) + MMF (2,000 mg)	TAC (6–8 ng/mL) + MMF (2,000 mg)	HPLC	Alemtuzumab	1 year	NA
Silva et al. 2013 ⁷⁸	Conversion from TAC to SRL	SRL (8 and 12 ng/mL) + EC-MPS (1,440 mg) + STER	TAC (5 and 15 ng/mL) + EC-MPS (1,440 mg) + STER	HPLC	Basiliximab	3 months	NA
Budde et al. 2012 ⁷³ Budde et al. 2011 ⁹²	Conversion from CsA to EVR	EVR (6–10 ng/mL) + MPS + STER (prednisolone ≥5 mg)	CsA (100–150 ng/mL) + MPS (1,440 mg) + STER (prednisolone ≥5 mg)	NR	Basiliximab	4.5 months	NA
Mjornstedt et al. 2012 ⁸⁰	Conversion from CsA to EVR	EVR (6–10 ng/mL) + EC-MPS (1,440 mg) + STER	CsA (C2 target 600–800 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	7 weeks	NA

Table E-5. Study design characteristics of conversion studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Nafar et al. 2012 ⁸¹	Conversion from CsA to SRL	SRL (8–15 ng/mL) + CsA changed to MMF in the 4 th month + STER (5 mg) administered during the first 3 months	CsA (150–250 ng/mL) + MMF (1,000–2,000 mg) + STER	NR	NR	4 months	Excluded DGF
Heilman et al. 2011 ⁷⁹	Conversion from TAC to SRL	SRL (8 ng/mL) + MMF (1,000 mg) + rapid STER withdrawal	TAC (5–8 ng/mL) + MMF (2,000 mg) + rapid STER withdrawal	NR	rATG	1 month	NA
Holdaas et al. 2011 ²²	Conversion from CNI to EVR	Conversion from CNI to EVR (8–12 ng/mL) + prior therapy (could include MPA, AZA and/or STER)	CsA (C2 target ≥400 ng/mL) or TAC (≥4 ng/mL) + prior therapy (could include MPA, AZA, and/or STER)	NR	NR	Minimum 6 months	NA
Rostaing et al. 2011 ⁹¹	Conversion from CNI to belatacept	Belatacept (10–12 µg/mL) + MMF, MPS, SRL or AZA	CsA (100–250 ng/mL) or TAC (5–10 ng/mL) + MMF, MPS, SRL or AZA	NR	NR	During 28-day period	NA
Weir 2011 ⁷⁵	Conversion from CNI to MMF	SRL (2.9 mg at 24 months) + MMF + STER	CsA (240.4 mg at 24 months) or TAC (7.1 mg at 24 months) + MMF + STER	NR	ATG: 105 Basiliximab: 80 Daclizumab: 32 Muromonab-CD3: 1	30–180 days	NA
Guba et al. 2010 ⁸²	Conversion from CsA to SRL	SRL (5–10 ng/mL) + MMF (1,500 mg) + STER	CsA (100–150 ng/mL) + MMF (2,000 mg) + STER	NR	ATG-F	10–24 days	Excluded PRA >30% and persistent DGF
Bemelman et al. 2009 ⁸³	Conversion from CsA to MPS or EVR	MPS (>2 mg) or EVR (target AUC 12–150 mg h/L) + STER	CsA (target AUC 120–3,250 µg h/L) + STER	NR	Basiliximab	6 months	Excluded PRA >50%
Schena et al. 2009 ⁷⁶	Conversion from CNI to SRL	SRL + MMF or AZA +STER	CsA or TAC + MMR or AZA +STER	HPLC (SRL) IA (CNI)	NR	Minimum 6 months	NA
Lebranchu et al. 2011 ¹²⁵ Lebranchu 2009 ⁸⁴	Conversion from CsA to SRL	SRL (5–10 ng/mL) + MMF + STER	CsA (C2 target 500–800 ng/mL) + MMF +STER	NR	Daclizumab	3 months	Excluded PRA >30%, living donors
Durrbach et al. 2008 ⁸⁵	Conversion from CsA to SRL	SRL (10–20 ng/mL) + MMF + STER	CsA (75–200 ng/mL) + MMF + STER	NR	ATG	NR	Excluded PRA >50%
Barsoum et al. 2007 ⁸⁶	Conversion from CsA to SRL	SRL (11.4±2.6 ng/mL) + MMF + STER	CsA (811±137.5 ng /mL) + MMF + STER	NR	NR	3 months	Excluded deceased donors

Table E-5. Study design characteristics of conversion studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Dudley et al. 2005 ⁹⁰	Conversion from CsA to MMF	MMF (2,000 mg) + STER (10 mg)	CsA (\geq 80 ng/mL)	NR	NR	10 weeks	NA
Watson et al. 2005 ⁷⁴	Conversion from CNI SRL	SRL (5–15 ng/mL) + AZA or mycophenolic acid + STER	CsA or TAC + AZA or mycophenolic acid + STER	HPLC	NR	Minimum 6 months	NA
Bakker et al. 2003 ⁸⁷	Conversion from CsA to AZA	AZA (2–2.5 mg/kg) + STER	CsA (5 mg/kg) + STER	NR	NR	3 months	NA
MacPhee et al. 1998 ⁸⁸	Conversion from CsA to AZA	AZA (1.6–1.9 mg/kg) + STER (10 mg)	CsA (2.5–3 mg/kg) + STER (10 mg)	IA/FPIA	NR	1 year	NA
Hilbrands et al. 1996 ⁸⁹	Conversion from CsA to AZA	AZA (3 mg/kg) + STER (10 mg)	CsA (100–200 ng./mL) + STER withdrawn	NR	ATG	3 months	NA

AZA=azathioprine; ATG=antithymocyte globulin; C2=2 hour post CsA dosage level; CNI=calcineurin inhibitors; CsA=cyclosporine; DGF=delayed graft function; EC-MPS=enteric-coated mycophenolate sodium; EVR=everolimus; FPIA=fluorescence polarization immunoassay; h/L=hectoliter; HPLC=high performance liquid chromatography; IA=immunoassay; mg=milligram; MMF=mycophenolate mofetil group; MPA=medroxyprogesterone acetate; MPS=mycophenolate sodium; NA=not applicable; ng/mL=nanogram per milliliter; NR=not reported; PRA=panel reactive antibody; STER=steroid; SRL=sirolimus; TAC=tacrolimus; μ g=micrograms

Table E-6. Study population characteristics of conversion studies

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Bensal et al. 2013 ⁷²	Conversion from CNI to SRL	India	31	29	Living	34 vs. 30	87%	100% Asian	NR
Chhabra et al. 2013 ⁷⁷	Conversion from TAC to SRL	USA	123	64	Deceased: 57 Living related: 76 Living unrelated: 55	49 vs. 49	57%	51%	13% overall
Silva et al. 2013 ⁷⁸	Conversion from TAC to SRL	Brazil	97	107	Deceased: 146 Living: 151	44 vs. 44	69%	57%	NR
Budde et al. 2012 ⁷³	Conversion from CsA to EVR	Germany	155	146	Deceased: 220 Living related: 57 Living unrelated: 23	46 vs. 46	63%	97%	NR
Mjornstedt et al. 2012 ⁸⁰	Conversion from CsA to EVR	Europe	102	100	Deceased: 144 Living: 58	55 vs. 53	71%	99%	NR
Nafar et al. 2012 ⁸¹	Conversion from CsA to MMF	Iran	50	50	Living	38 vs. 42	55%	100% (Iranian)	NR
Heilman et al. 2011 ⁷⁹	Conversion from TAC to SRL	USA	62	60	Deceased	52 vs. 54	62%	77%	9% overall
Holdaas et al. 2011 ²²	Conversion from CNI to EVR	Worldwide	127	123	Deceased: 154 Living related: 93 Missing: 3	49 vs. 48	67%	72%	NR
Rostaing et al. 2011 ⁹¹	Conversion from CNI to belatacept	France	84	89	Deceased: 86 Living: 83	45 vs. 44	73%	56%	NR
Weir 2011 ⁷⁵	Conversion of CNI to SRL	USA	148	151	Deceased: 180 Living related: 79 Living unrelated: 40	48 vs. 48	63%	50%	NR
Guba et al. 2010 ⁸²	Conversion from CsA to SRL	Germany	69	71	Brain death: 125 Living: 15	47 vs. 47	68%	99%	24% overall
Bemelman et al. 2009 ⁸³	Conversion from CsA to MPS or EVR	Netherlands	74 (MPS 36, EVR 38)	39	Deceased: 63 Living: 50	52 (MPS) vs. 49 (EVR) vs. 51 (CsA)	57%	86%	NR
Schena et al. 2009 ⁷⁶	Conversion from CNI to SRL	Worldwide	555	275	Deceased: 520 Living: 303	44 vs. 43	70%	66%	NR
Lebranchu et al. 2011 ¹²⁵ Lebranchu 2009 ⁸⁴	Conversion from CsA to SRL	France	95	97	Deceased	46 vs. 47	71%	NR	14% overall
Durrbach et al. 2008 ⁸⁵	Conversion from CsA to SRL	France	33	36	Living	52 vs. 57	NR	NR	38% overall
Barsoum et al. 2007 ⁸⁶	Conversion from CsA to SRL	Egypt	76	37	Living	45 vs. 44	65%	NR	29% overall

Table E-6. Study population characteristics of conversion studies (continued)

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Dudley et al. 2005 ⁹⁰	Conversion from CsA to MMF	United Kingdom	73	70	Deceased: 119 Living: 24	43 vs. 45	62%	NR	NR
Watson et al. 2005 ⁷⁴	Conversion from CNI to SRL	United Kingdom	19	19	Deceased: 28 Living: 10	47 vs. 48	82%	NR	NR
Bakker et al. 2003 ⁸⁷	Conversion from CsA to AZA	Netherlands	60	68	Deceased	46 vs. 43	62%	NR	NR
MacPhee et al. 1998 ⁸⁸	Conversion from CsA to AZA	Scotland	102	114	Deceased: 194 Living: 22	41 vs. 39	59%	NR	NR
Hilbrands et al. 1996 ⁸⁹	Conversion from CsA to AZA	Netherlands	60	60	Deceased	43 vs. 43	63%	NR	NR

CNI=calcineurin inhibitors; CsA=cyclosporine; EVR=everolimus; MMF=mycophenolate mofetil group; MPS=mycophenolate sodium; NR=not reported; SRL=sirolimus; TAC=tacrolimus

Table E-7. Clinical outcomes of conversion studies

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite ¹ (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Bensal et al. 2013 ⁷²	6 months	Target C0 TAC 6 to 8 ng/mL; CsA 150 to 250 ng/mL; SRL 8 to 15 ng/mL	NR	CNI: 2 SRL: 2	Authors report no difference between groups; data not reported	Authors report no difference between groups; data not reported	Mean eGFR CNI: 80.6±16.5 mL/min/MDRD SRL: 88.9±11.8	CNI: 1.14±0.17 mg/dL SRL: 0.99±0.11	SRL group had a mean gain of eGFR of 12 mL/min
Chhabra et al. 2013 ⁷⁷	2 years	Target C0 TAC 6 to 8 ng/mL SRL C0 6 to 8 ng/mL	NR	TAC: 7 SRL: 4	TAC: 2 SRL: 3	TAC: 0 SRL: 4	Mean eGFR at 12 months TAC: 66.6 mL/min/MDRD SRL: 67.5	NR	NR
Silva et al. 2013 ⁷⁸	2 years	NR	NR	TAC: 62 SRL: 22	TAC: 4 SRL: 1	TAC: 9 SRL: 3	Mean eGFR TAC: 70.7±25.1 mL/min/MDRD SRL: 66.2±25.3	TAC: 1.3±0.3 mg/dL SRL: 1.4±0.4	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite ¹ (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Budde et al. 2012 ⁷³ ZUES trial 3 year followup	3 years	Target C0 CsA 100 to 150 ng/mL EVR: 6 to 10 ng/mL	CsA: 23 EVR: 46	CsA: 7 EVR: 20	CsA: 1 EVR: 1	CsA: 3 EVR: 3	<u>24 months</u> CsA: 62.4 mL/min/Nankivell (95% CI 58.7 to 66.1) EVR: 70.0 (95% CI 66.6 to 73.5) <u>36 months</u> CsA: 61.0 (95% CI 56.4 to 65.6) EVR: 68.5 (95% CI 64.0 to 73.0)	NR	NR
Budde et al. 2011 ⁹² ZEUS trial	1 year	Target C0 CsA 100 to 150 ng/mL EVR: 6 to 10 ng/mL	CsA: 42 EVR: 39	CsA: 22 EVR: 23	CsA: 0 EVR: 0	CsA: 1 EVR: 0	CsA: 61.9 mL/min/Nankivell (95% CI 59.0 to 64.9) EVR: 71.8 (95% CI 68.9 to 74.6) Mean difference: -9.8 (95% CI -12.2 to -7.5, p<0.001)	NR	NR
Mjornstedt et al. 2012 ⁸⁰	1 year	At months 6 and 12 all patients within C0 target range from EVR (6 to 10 ng/mL) and CsA (117 ng/mL at 6 months; 105 at 12 months)	CsA: 12 EVR: 29	CSA: 11 EVR: 28	CsA: 0 EVR: 0	CsA: 2 EVR: 2	CsA: 47.8±15.4 mL/min/ measured GFR EVR: 51.2±14.1	CsA: 132±45 µmol/L EVR: 122±35	NR
Nafar et al. 2012 ⁸¹	4 years	SRL target C0 levels 8 ng/mL to 15 ng/mL CsA C0 levels 150 ng/mL to 250 ng/mL	NR	CsA: 9 pts. (34 episodes) SRL: 4 pts. (20 episodes)	Authors report no significant difference between groups; data reported in figure	Authors report no significant difference between groups; data reported in figure	<u>At 1 year</u> CsA: 73.2±19.2 mL/min/ Cockcroft SRL: 82.3±24.3 <u>At 4 years</u> CsA: 70.3±23.6 SRL: 79.8±22.3	<u>At 1 year</u> CsA: 1.4±0.35 mg/dL SRL: 1.26±0.32 <u>At 4 years</u> CsA: 1.57±0.33 SRL: 1.24±0.24	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite ¹ (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Heilman et al. 2011 ⁷⁹	2 years	SRL level at 1 year 9.8±3.6 ng/dL TAC level at 1 year 6.9±4.6 ng/dL	NR	TAC: 3 SRL: 8	<u>At 1 year</u> TAC: 0 SRL: 0 <u>At 2 year</u> TAC: 2 SRL: 1	<u>At 1 year</u> TAC: 0 SRL: 0 <u>At 2 year</u> TAC: 2 SRL: 1	<u>At 1 year</u> TAC: 62.7±26.5 mL/min/ iothalomate clearance SRL: 57.4±20.7 <u>At 2 years</u> TAC: 62.8±21.6 SRL: 64.3±29.0	<u>At 1 year</u> TAC: 1.39±0.81 mg/dL SRL: 1.26±0.37 <u>At 2 years</u> TAC: 1.26±0.36 SRL: 1.39±0.54	Total withdraws TAC: 11 SRL: 39, 23 of which were for drug side effects
Rostaing et al. 2011 ⁹¹	1 year	BEL C0 level maintained at 10 to 12 µg/ml; CsA C0 serum level maintained at 100 to 250 ng/ml TAC at 5 to 10 ng/ml	NR	CNI: 0 BEL: 6	CNI: 0 BEL: 0	CNI: 2 BEL: 0	CNI: 56.5±14.42 mL/min/MDRD BEL: 60.5±11.01	NR	NR
Weir et al. 2011 ⁷⁵	2 years	Authors report that mean C0 levels of TAC remained stable over study and CsA levels decreased due to dosage reduction	<u>12 months</u> CNI: 29 SRL: 36 <u>24 months</u> CNI: 42 SRL: 50	CNI: 9 SRL: 11	CNI: 4 SRL: 3	CNI: 5 SRL: 0	<u>1 year</u> CNI: 71.5±21.2 ml/min/ Nankivell SRL: 74.6±17.9 <u>2 years</u> CNI: 71.2±23.4 SRL: 75.5±19.2	<u>1 year</u> CNI: 145.0±96.5µmol/L SRL: 126.2±82.8 <u>2 years</u> CNI: 151.8±117.0 SRL: 127.1±83.9	Creatinine Clearance <u>1 year</u> CNI: 58.0±23.3 mL/min SRL: 61.9±20.1 <u>2 years</u> CNI: 56.9±23.0 SRL: 62.3±22.1
Guba et al. 2010 ⁸²	1 year	Authors report C0 level generally met CsA C0: 100 to 150 ng/mL SRL: 5 to 10 ng/mL	CsA: 23 SRL: 35	CsA: 11 SRL: 12	CsA: 3 SRL: 1	CsA: 1 SRL: 1	CsA: 53.4±18.0 mL/min/ Nankivell SRL: 64.5±25.2	SRL: 1.51±0.59 (mg/dL) CsA: 1.87±0.98 (mg/dL)	Drug withdrawals significantly higher in SRL group (36.2%) than in CsA group (19.0%)

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite ¹ (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Bemelman et al. 2009 ⁸³	2 years	Target CsA AUC ₁₂ 3,250 µg·h/L EVR 150 mg·h/L	NR	CsA: 1 MPS: 8 EVR: 0	NR	NR	Mean eGFR at baseline (for all groups) 58±18 mL/min/MDRD <u>At follow-up</u> CsA: 44±15 MPS: 56±23 EVR: 55±20	<u>At conversion</u> ² CsA: 124±11 µmol/L MPS: 116±11 EVR: 118±12 <u>At follow-up</u> ² CsA: 139±14µmol/L MPS: 135±21 EVR: 110±7	NR
Schena et al. 2009 ⁷⁶ CONVERT Trial at 24 months followup	2 years	Target C0 CsA 50 to 250 ng/mL TAC 4 to 10 ng/ng/mL; SRL 8 to 20 ng/mL	CNI: 40 SRL: 89	CNI: 19 SRL: 44	CNI: 26 SRL: 58	CNI: 12 SRL: 32	<u>Pts baseline GFR >40 mL/min (n=743)</u> CNI: 52.1 SRL 53.7 Diff: 1.6 (95% CI: -1.43 to -4.6) <u>Pts baseline GFR 20 to 40 mL/min</u> CNI: 17.9 SRL: 21.7 Diff: 3.8 (95% CI: -12.27 to -6.91)	<u>Mean urinary protein/creatinine ratio</u> CNI: 0.22±0.40 SRL:0.72±1.50	NR
Schena et al. 2009 ⁷⁶ CONVERT Trial at 12 months followup	1 year	NR	CNI: 11 SRL: 36	CNI: 4 SRL: 17	CNI: 8 SRL: 27	CNI: 2 SRL: 14	<u>Pts baseline GFR >40 mL/min/Nankivell (n=743)</u> CNI: 57.7 SRL: 59.0 Diff: 1.3 (95% CI: -1.06 to -3.69) <u>Pts. baseline GFR 20 to 40 mL/min (n=87)</u> CNI: 27.2 SRL: 24.6 Diff: -2.6 (95% CI: -12.27 to -6.91)	<u>Mean urinary protein/creatinine ratio</u> CNI: 0.23±0.25 SRL: 0.36±0.53	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite ¹ (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Lebranchu et al. 2011 ¹²⁵	4 year	Target CsA C2 500 to 800 ng/mL	NR	CsA: 2 SRL: 2	CsA: 0 SRL: 1	CsA: 2 SRL: 2	CsA: 51.4 mL/min/MDRD (95% CI 47.9 to 54.9) SRL: 58.7 (95% CI 55.1 to 62.4)	NR	NR
Lebranchu et al. 2009 ⁸⁴	1 year	Target CsA C2 500 to 800 ng/mL	NR	CsA: 8 SRL: 16	CsA: 0 SRL: 1	CsA: 0 SRL: 0	CsA: 53.9±51 mL/min/MDRD SRL: 61.2±58	CsA: 132.3 µmol/L (126.1 to 138.5) SRL: 117.4 (110.7 to 124.2)	NR
Durrbach et al. 2008 ⁸⁵	6 months	At 6 months, SRL C0 level 13.0±4.0 ng/mL at 6.8±4.9 g/d CsA dose 233±77 mg/d	NR	SRL: 4 CsA: 3	SRL: 4 CsA: 1	SRL: 1 CsA: 0	SRL: 44.7±16.6 mL/min/ Cockcroft CsA: 41.9±15.2 mL/min	SRL: 171±53 µmol/L CsA: 171±65	Delayed graft function: SRL: 15 CsA: 11 Withdrawal SRL: 16 CsA: 6
Barsoum et al. 2007 ⁸⁶	2 years	At 12 to 24 months, CsA C2 level 1,000 ng/mL; SRL C0 level 10 to 15 ng/mL	NR	SRL: 10 CsA: 7	SRL: 4 CsA: 4	SRL: 3 CsA: 3	Mean eGFR Baseline SRL: 61.85±10.45 mL/min/ MDRD CsA: 63.77±8.9 2 years SRL: 70.2 ±8.0 CsA: 55.86±7.8	SRL: 96.8 µmol/L CsA: 126.72	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite ¹ (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Dudley et al. 2005 ⁹⁰	1 year	Target CsA C0 at 12 months 117.0±49 ng/mL	NR	CsA: 0 MMF: 0	CsA: 4 MMF: 2	CsA: 0 MMF: 3	NR	Serum creatinine clearance <u>6 months</u> CsA: 244.1 (±55) µmol/L (increase of 22.3 from baseline) MFF: 200.7 (±61) (decrease of -21 from baseline) <u>12 months</u> CsA: 245.1 (±50) (increase of 22.2) from baseline MMF: 198.0 (±53) (decrease of -24.9 from baseline)	Number of responders (experienced a significant improvement in renal function) <u>6 months</u> CsA: 18 MMF: 36 <u>12 months</u> CsA: 21 MMF: 30
Watson et al. 2005 ⁷⁴	1 year	Median daily dose of SRL at 12 months 2.5 mg; whole blood levels 8.5 ng/mL (4.9 to 12.5) Median C0 TAC: 10.6 ng/mL; median CsA: 187 ng/mL	NR	CNI: 0 SRL: 0	NR	NR	Baseline GFR CNI: 36.1 mL/min SRL: 37.8 Mean difference between groups at <u>3 months</u> : 7.9 mL/min (95% CI 4.1 to 11.7, p=<0.001); at <u>12 months</u> : 12.9 (95% CI 6.1 to 19.7, p=<0.001) This indicates a GFR improvement of 8.5 ml/min among SRL group and a decline of 4.3 in the CNI group.	Mean difference between groups: -67 µmol/L (-148 to 14)	1 patient in each group returned to dialysis
Bakker et al. 2003 ⁸⁷	15 years	Mean dose of CsA 5.1±1.4 mg/kg	NR	CsA: 2 AZA: 3	CsA: 24 AZA: 14	CsA: 29 AZA: 27	CsA: 59.3 mL/min/ Nankivell SRL: 71.7 Diff: 15.7 (95% CI: 0 to 30.6)	NR	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite ¹ (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Bakker et al. 2003 ⁸⁷	≤10 years	Mean dose of CsA 5.1±1.4 mg/kg	NR	See above	CsA: 17 AZA: 9	CsA: 19 AZA: 16	<u>3 months</u> CsA: 56.5 mL/min/ Nankivell SRL: 53.5 Diff: 3.0 (95% CI -2.6 to 8.6) <u>1 year</u> CsA: 55.7 SRL: 72.9 Diff: 17.1 (95% CI 11.6 to 22.7) <u>10 years</u> CsA: 52.8 SRL: 71.7 Diff: 19.0 (95% CI: 10.0 to 27.8)	NR	NR
MacPhee et al. 1998 ⁸⁸	10 year	Target levels of CsA (97±34 nmol/L) achieved at dose 2.5 to 3.0 mg/kg Target maintenance dose of AZA 1.6 to 1.9 mg/kg	NR	CsA: 17 AZA: 16	CsA: 48 AZA: 39	CsA: 12 AZA: 6	NR	CsA: 153 µmol/L AZA: 153 µmol/L	NR

Table E-7. Clinical outcomes of conversion studies (continued)

Reference	Length of Follow-up	Achievement of CNI Target Levels	Treatment Failure Composite ¹ (n)	Biopsy Proven Acute Rejection (n)	Graft Loss (n)	Patient Death (n)	Mean eGFR or Creatinine Clearance (mL/min) (method)	Mean Serum Creatinine	Other
Hilbrands et al. 1996 ⁸⁹	1 year	CsA C0 levels 100 to 200 ng/ml	NR	CsA: 20 AZA: 16	CsA: 1 AZA: 1	CsA: 1 AZA: 1	NR	Mean creatinine clearance <u>At 3 months</u> CsA: 57 (40 to 69) ml/min AZA: 52 (42 to 66) <u>At 1 year</u> CsA: 53 (43 to 67) 64 (53 to 84)	Quality of Life at 1 year ³ <u>Median SIP score</u> CsA: 3.8 (1.3 to 6.5) AZA: 3.5 (0.5 to 10.4) <u>Median ABS score</u> CsA: 7.5 (6 to 8.5) AZA: 7 (5.5 to 8) <u>Median CES-D score</u> CsA: 1 (0 to 4) AZA: 1 (0 to 5.5)

¹ Composite variable defined as biopsy-proven acute rejection, graft loss, death and loss to follow-up, discontinuation due to lack of efficacy or toxicity, conversion to another regimen up to or at 12 month after transplantation.

² The mean creatinine levels and standard deviations were estimated based on data presented in a figure.

³ Lower scores on the ABS, CES-D, and SIP indicate better quality of life.

ABS=affect balance scale; AUC=area under the curve; AZA=azathioprine; BEL=belatacept; C0=CsA trough level; C2=2 hour post CsA dosage level; CES-D=Center for Epidemiologic Studies Depression Scale; CI=confidence interval; CNI=calcineurin inhibitors; CsA=cyclosporine; EVR=everolimus; g/d=gram per day; GFR/eGFR=glomerular filtration rate/estimated glomerular filtration rate; h/L=hectoliter; k/L=kiloliter; MDRD=modification of diet in renal disease; mg/kg=milligram per kilogram; mL/min=milliliter per minute; MMF=mycophenolate mofetil group; MPS=mycophenolate sodium; ng/mL=nanogram per milliliter; nmol/L=nanogram per liter; NR=not reported; SIP=sickness impact profile; SRL=sirolimus; TAC=tacrolimus; μ mol/L=micromoles per liter

Table E-8. Adverse events reported in conversion studies

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Bensal et al. 2013 ⁷²	Conversion from Control Regimen to SRL	Authors report no difference between groups 9 (31%) in CNI group vs. 7 (22.6%) in SRL group; $p=0.459$	NR	Herpes simplex virus infection: 1 patient in CNI group Herpes zoster: 1 patient in SRL group Fulminant bacterial pneumonia: 1 patient in SRL group 0 CMV or BK Respiratory infection: 1 patient in each group Skin infection: 1 patient in CNI group	0 patients	No between-group differences	NR	Tuberculosis: 1 patient in CNI group Enthesitis: 4 patients in the SRL group. Seizure: 1 SRL patient with a history of seizures developed a seizure during treatment. Aphthous stomatitis: 1 patient in SRL group
Chhabra et al. 2013 ⁷⁷	Conversion from TAC to SRL	Authors report no difference between groups, data not included	TAC 4/123 vs. SRL 1/64	CMV: TAC 7 vs. SRL 3 BK: TAC 5 vs. SRL 2 Pneumonia: TAC 3 vs. SRL 1 Herpes: TAC 4 vs. SRL 2 Nasopharyngitis: TAC 5 vs. SRL 1 Cyclosporidiosis: TAC 1 vs. SRL 0 Cellulitis: TAC 2 vs. SRL 0 Histoplasmosis: TAC 0 vs. SRL 1 UTI: TAC 20 vs. SRL 7	Authors report no difference between groups, data not included	TAC 11 vs. SRL 5	Hyperlipidemia higher in SRL vs. TAC group Cholesterol-lowering medication use: SRL: 45% CNI: 22%	Histoplasmosis: TAC 0 SRL 1 Cyclosporidiosis: TAC 1 SRL 0

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Silva et al. 2013 ⁷⁸	Conversion from TAC to SRL	NR	Kaposi's sarcoma: TAC: 1/107 Emryonal testicular carcinoma: TAC: 2/107	TAC group: Polyomavirus nephropathy: 2/107 (2%) CMV Virus: months 4-24 SRL: 5% TAC: 4% Herpes zoster: months 4-24 SRL: 4% TAC: 7% Polyomavirus: months 4-24 SRL: 3% TAC: 4% Pneumonia: TAC: 2 (2%)	2 patients suffered a cardiovascular event leading to death. SRL: 1/97 TAC: 1/107	SRL: 3 (3%)	Blood Pressure: No difference Dyslipidemia SRL: 6 TAC: 3 Total cholesterol (mg/dL) SRL: 219 TAC: 181 Triglycerides, HDL, VLDL, LDL higher in SRL group	6 combined deaths recorded in SRL and TAC groups (2 due to infection and 1 due to cardiovascular event each) SRL: zygomycosis Diarrhea TAC: 2/107 (2%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Budde et al. 2012 ⁷³ FOLLOW-UP: Budde et al. 2011 ⁹²	Conversion from CsA to EVR	Diabetes mellitus CsA: 15 (10%); 20 (13%) p=0.4667	13 malignancies were reported within 36 months after randomization Basalioma CSA: 6/145 EVR: 3/155 Squamous cell carcinoma CSA: 1/145 EVR: 2/155 Spinalioma (left arm) CSA: 1/145 Post-transplant lymphoproliferative disease EVR: 1/155	Herpes virus CsA: 8 (6%); EVR: 21 (14%); p=0.0198 Pneumocystis jirovecii pneumonia CsA: 1 (<1%); EVR: 1 (<1%); p=1.0 BK virus CsA: 5 (3%); EVR: 11 (7%); p=0.20 Cytomegalovirus CsA: 27 (19%); EVR: 28 (18%) p=1.0 Pneumonia CsA: 12 (8%); EVR: 10 (6%); p=0.6590 Infections during months 12–24 CSA: 30 (20.7%); EVR: 35 (22.6%); p=0.69 Infections during months 24–36 CSA: 29 (20.0%); EVR: 31 (20.0%); p>0.99 Overall rate of infections by month 36 CSA: 49 (33.8%); EVR: 55 (35.5%); p=0.76 UTI infection CsA: 77 (53%); EVR: 89 (57%); p=0.4866	Myocardial infarction CsA: 1 (Death of patient not related to drug)	CsA: 24 (17%) EVR: 24 (15%); p=0.8752	Hyperlipidemia CsA: 15 (10%) EVR: 22 (14%) p=0.3804 Hypercholesterolaemia CsA: 40 (28%) EVR: 45 (29%) Hypertriglyceridaemia CsA: 5 (3%) EVR: 10 (6%) Hypertension CsA: 20 (14%) EVR: 8 (12%) p=0.6055 Hypotension CsA: 32 (22%) EVR: 22 (114%) p=0.0977	Nasopharyngitis CsA: 38 (26%) EVR: 43 (28%) p=0.7957 Aphthous stomatitis CsA: 4 (3%) EVR: 26 (17%) p<0.0001 Diarrhea CsA: 39 (27%) EVR: 56 (36%) p=0.1063 Impaired healing CsA: 5 (3%) EVR: 6 (4%); p=1.0

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Mjornstedt et al. 2012 ⁸⁰	Conversion from CsA to EVR	NR	Malignant parathyroid tumor EVR: 1 Adenocarcinoma of the prostate EVR: 1 Squamous cell carcinoma CsA: 1 Testicular cancer CsA: 1	Urinary tract infection EVR: 15 (14.7%) CsA: 28 (28.0%) Polyoma virus infection EVR: 2 (2.0%) CsA: 1 (1.0%) CMV EVR: 9 (8.8%) CsA: 13 (13.0%) Herpes simplex EVR: 5 (4.9%) CsA: 1 (1.0%) Pneumonia EVR: 12 (11.8%) CsA: 2 (2.0%) Upper respiratory tract infection EVR: 5 (4.9%) CsA: 4 (4.0%) Herpes zoster EVR: 1 (1.0%) CsA: 6 (6.0%) Oral candidiasis EVR: 5 (4.9%) CsA: 2 (2.0%) BK virus nephropathy EVR: 1 CsA: 2 Sepsis EVR: 5 Gastroenteritis EVR: 5	NR	EVR: 5 (4.9%)	Hyperlipidemia EVR: 13 (12.7%) CsA: 9 (9.0%) Hypercholesterolemia EVR: 10 (9.8%) CsA: 2 (2.0%) Blood pressure lower in EVR vs. CsA	Edema EVR: 30 (29.4%) CsA: 21 (21.0%) <u>Anemia</u> EVR: 17 (16.7%) CsA: 6 (6.0%) <u>Leukopenia</u> EVR: 14 (13.7%) CsA: 11 (11.0%) <u>Acne</u> EVR: 13 (12.7%) CsA: 2 (2.0%) <u>Mouth ulceration</u> EVR: 13 (12.7%) CsA: 1 (1.0%) <u>Lymphocele</u> EVR: 10 (9.8%) CsA: 6 (6.0%) <u>Dermatitis</u> EVR: 9 (8.8%) CsA: 5 (5.0%) <u>Cough</u> EVR: 7 (6.9%) CsA: 4 (4.0%) <u>Headache</u> EVR: 6 (5.9%) CsA: 4 (4.0%) <u>Hypokalemia</u> EVR: 6 (5.9%) <u>Venous thrombosis</u> EVR: 6 (5.9%) CsA: 3 (3.0%) <u>Myalgia</u> EVR: 5 (4.9%) CsA: 2 (2.0%) <u>Sinusitis</u> EVR: 5 (4.9%) CsA: 1 (1.0%) <u>Diarrhea</u> EVR: 5(4.9%) CsA: 11(11.0%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
								<u>Fatigue</u> EVR: 2 (2.0%) CsA: 7 (7.0%) <u>Hirsutism</u> EVR: 1 (1.0%) CsA: 6 (6.0%) <u>Arthralgia</u> EVR: 4 (3.9%) CsA: 5 (5.0%) <u>Dizziness</u> EVR: 1 (1.0%) CsA: 5 (5.0%) <u>Hydronephrosis</u> EVR: 4 <u>Pyelonephritis</u> CsA: 3
Nafar et al. 2012 ⁸¹	Conversion from CsA to MMF	No significant findings. Fasting blood glucose, (mg/dL) 1 year followup values: SRL: 96 CsA: 105	NR	NR	CsA: 4 patients suffered cardio events coupled with sepsis leading to death.	NR	Serum cholesterol (mg/dL) SRL: 194 CsA: 190 Serum triglyceride (mg/dL) SRL: 205 CsA: 189	Hospitalization – 4 year period SRL: 52 CsA: 44
Heilman et al. 2011 ⁷⁹	Conversion from TAC to SRL; rapid STER withdrawal for all patients	NR.	Cancer SRL: 1	CMV SRL: 8 TAC: 8 BK virus Nephropathy SRL: 2 TAC: 3 Pneumonitis SRL: 2 Fever SRL: 1	NR	SRL: 4	Hyperlipidemia SRL: 4 No difference in blood pressure	Oral ulcers SRL: 7 Edema SRL: 3 Cytopenia SRL: 2 Rash SRL: 2 IFTA TAC: 2

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Holdaas et al. 2011 ²²	Conversion from CNI to EVR	6/127 vs. 4/123	9 vs. 7	Any infection: 83 vs. 75 UTI: 22 vs. 13 Upper respiratory tract: 15 vs. 16	NR	21 vs. 11	Cholesterol, triglycerides, hyperlipidemia higher in intervention group; no difference for hypertension	Higher incidence of GI, anemia, edema, pyrexia, in intervention group

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Rostaing et al. 2011 ⁹¹	Conversion from CNI to Belatacept	Diabetes Belatacept: 7 (8%) CNI: 10 (11%)	Basal cell carcinoma Belatacept: 1 (1%) CNI: 2 (2%) Kaposi's sarcoma Belatacept: 1 (1%)	Herpes infections Belatacept: 4 (5%) CNI 3 (3%) <u>BK polyoma virus</u> Infection Belatacept: 3 (4%) <u>Polyomavirus associated nephropathy</u> Belatacept: 1 (1%) <u>CMV infection</u> Belatacept: 2 (2%) CNI: 2 (2%) <u>Kaposi's sarcoma</u> Belatacept: 1 (1%) <u>Urinary tract infection</u> Belatacept: 2 (2%) <u>Total fungal Infections</u> Belatacept: 11 (13%) CNI: 3 (3%) <u>Tinea versicolor</u> Belatacept: 5 (6%) <u>Fungal infection</u> Belatacept: 1 (1%) CNI: 1 (1%) <u>Onychomycosis</u> Belatacept: 1 (1%) CNI: 1 (1%) <u>Body tinea</u> Belatacept: 1 (1%) <u>Skin candida</u> Belatacept: 1 (1%) <u>Vulvovaginal mycotic infection</u> Belatacept: 1 (1%) <u>Pyrexia</u> Belatacept: 3 (4%)	Myocardial infarction CNI: (1/89)		BP over the 12 months Belatacept: 4.0/3.5 mmHg CNI group 1.6/1.7 mmHg	Congenital, Familial, and Metabolic Disorders Belatacept: 3 (4%) CNI: 3 (3%) Other causes Belatacept: 35 (42%) CNI: 43 (48%) Glomerulonephritis Belatacept: 23 (27%) CNI: 14 (16%) Polycystic kidneys Belatacept: 9 (11%) CNI: 9 (10%) Renovascular/hypertensive nephrosclerosis Belatacept: 7 (8%) CNI: 10 (11%) Pyelonephritis Belatacept: 2 (2%) CNI- 1 (1%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Weir 2011 ⁷⁵	Conversion from CNI to SRL + MMF	Diabetes CNI: 2 (6%)	Malignancies SRL: 7 (4.7%) CNI: 10 (6.5%)	Aspergillus CNI: 1 (0.9%) BK virus infection CNI: 9 (6%) Candida SRL: 8 (5.4%) CNI: 12 (7.8%) CMV SRL: 7 (4.7%) CNI: 15 (9.8%) Herpes simplex SRL: 6 (4.1%) CNI: 1 (0.7%) Herpes zoster SRL: 12 (8.1%) CNI: 8 (5.2%) Pneumocystis SRL: 2 (1.4%) Cryptococcus CNI: 1 (0.7%)	Pulmonary embolism CNI: 1 (lead to death) Cardiac arrest CNI: 1 (lead to death)	SRL: 3 (4.4%)	Diastolic blood pressure was lower after 24 months in SRL group Hyperlipidemia SRL: 120 (81.1%) CNI: 97 (63.4%) Hypertension SRL: 30 (20.3%) CNI: 25 (16.3%)	Diarrhea SRL: 51 (34.5%) CNI: 50 (32.7%) Peripheral edema SRL: 42 (28.4%) CNI: 20 (13.1%) Leukopenia SRL: 36 (24.3%) CNI: 29 (19%) Mouth Ulceration SRL: 21 (14.2%) Urosepsis CNI: 1 (lead to death) Focal segmentation SRL: 2 (3%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Guba et al. 2010 ⁸²	Conversion from CsA to SRL	Diabetes mellitus SRL: 7.3% CsA: 5.6% p=0.7430	CsA: 4 (6%) patients; including renal cell cancer, colon cancer, squamous cell cancer of the nasal cavity, and non-Hodgkin lymphoma of the transplanted kidney. SRL: No cancers This between group difference was not significant; p=0.1198	CMV infection SRL: 7.3%; CsA: 28.2%; p=0.0016 Pneumonia SRL: 11.6%; CsA: 9.9%; p=0.7901 Urinary tract infections SRL: 18.8%; CsA: 29.6%; p=0.1691 Infections and infestations (overall) SRL: 52.2%; CsA: 60.6%; p=0.3942 Skin infections SRL: 8.70%; CsA: 1.41%; p=0.0608 Respiratory SRL: 13.0%; CsA: 7.0%; p=0.2711	Cardiac disorders SRL: 13.0%; CsA: 5.6%; p=0.1545	Proteinuria: SRL: 5 (7.3%) CsA: 1 (1.4%) (p=0.113)	Hyperlipidemia SRL: 20.3%; CsA: 7.0%; p=0.0269	Serious adverse events SRL: 53.6% CsA: 66.2% p=0.1675; severity similar in both groups <u>Lymphocele</u> SRL: 27.5% CsA: 23.9%; p=0.7005 <u>Gastrointestinal disorders (overall)</u> SRL: 29.0% CsA: 33.8%; p=0.5877 <u>Diarrhea</u> SRL: 13.0% CsA: 9.9%; p=0.6037 <u>Metabolism and nutrition disorders (overall)</u> SRL: 30.4% CsA: 29.6%; p=1.0 <u>Blood and lymphatic disorders (overall)</u> SRL: 26.1% CsA: 23.9%; p=0.8462 <u>Anemia</u> SRL: 13.0% CsA: 5.6%; p=0.1545 <u>Thrombopenia</u> SRL: 2.9% CsA: 4.2%; p=1.0 <u>Leucopenia</u> SRL: 10.1% CsA: 11.3%; p=1.0 <u>Vascular disorders (overall)</u> SRL: 10.1% CsA: 18.3%; p=0.2277 <u>Hypertonia</u> SRL: 0% CsA: 4.2%; p=0.2448

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
								<u>Skin and subcutaneous tissue disorders (overall)</u> SRL: 20.3% CsA: 7.0%; p=0.0269 <u>Acne</u> SRL: 7.25% CsA: 0%; p=0.0270 <u>Hepatobiliary disorders</u> SRL: 11.6% CsA: 9.9%; p=0.7901 <u>Nervous system disorders</u> SRL: 10.1% CsA: 9.9%; p=1.0
Bemelman et al. 2009 ⁸³ Interim report of 2 year study	Conversion from CsA to MPS or EVR	NR	Posttransplant lymphoproliferative disease EVR: 1	Cytomegalovirus disease CSA: 0(0%); MPS: 1(1%); EVR: 0(0%) Pneumonia CSA: 1(1%); MPS: 3(3%); EVR: 2(2%) Transplant pyelonephritis and urosepsis CSA: 1(1%); MPS: 0(0%); EVR: 5(5%) Lower urinary tract infection CSA: 2(2%); MPS: 3(3%); EVR: 9(6%) Flu-like syndrome EVR: 3(3%)	Cardio events CSA: 1(1%); MPS: 4(4%); EVR: 2(2%)	Not reported	No between group differences	Other (diarrhea, abdominal pain, varicella zoster, anemia, leucopenia) MPS: 7(7%) Other (abdominal pain, dysmenorrhea, urethral syndrome) EVR: 7(7%) Ankle edema CSA: 0(0%); MPS: 0(0%); EVR: 2(2%) Diarrhea CSA: 0(0%); MPS: 1(1%); EVR: 1(1%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Schena et al. 2009 ⁷⁶	Conversion from CNI to SRL	Frequency of diabetes mellitus SRL: 21 (4.7%) CNI: 30 (4.4%)	Malignancies, Total SRL: 21 (3.8%) CNI: 30 (11.0%) Skin carcinoma SRL: 12 (2.2%) CNI: 21 (7.7%)	Infection Pneumonia SRL: 70 (12.7%) CNI: 14 (5.1%) Herpes simplex SRL: 48 (8.7%) CNI: 12 (4.4%) Fever SRL: 113 (20.5%) CNI: 25 (9.2%)	NR	Proteinuria higher in the CNI vs. SRL group.	Hyperlipidemia SRL: 295 (53.5%) CNI: 72 (26.4%)	Other <u>Aphthous stomatitis</u> SRL: 23 (4.2%) CNI: 1 (0.4%) <u>Stomatitis</u> SRL: 21 (3.8%) CNI: 1 (0.4%) <u>Acne</u> SRL: 10 (1.8%) <u>Hyperlipidemia</u> SRL: 295 (53.5%) CNI: 72 (26.4%) <u>Diarrhea</u> SRL: 216 (39.2%) CNI: 63 (23.1%) <u>Anemia</u> SRL: 200 (36.3%) CNI: 45 (16.5%) <u>Peripheral edema</u> SRL: 176 (31.9%) CNI: 37 (13.6%) <u>Albuminuria</u> SRL: 130 (23.6%) CNI: 35 (12.8%) <u>Acne</u> SRL: 89 (16.2%) CNI: 11 (4.0%) <u>Thrombocytopenia</u> SRL: 77 (14.0%) CNI: 9 (3.3%) <u>Leukopenia</u> SRL: 74 (13.4%) CNI: 12 (4.4%) <u>Skin rash</u> SRL: 67 (12.2%) CNI: 11 (4.0%)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
								<u>Lactic dehydrogenase increased</u> SRL: 64 (11.6%) CNI: 3 (1.1%) <u>Hyperglycemia</u> SRL: 62 (11.3%) CNI: 18 (6.6%) <u>Hyperuricemia</u> SRL: 41 (7.4%) CNI: 42 (15.4%)
Lebranchu et al. 2011 ¹²⁵ Lebranchu 2009 ⁸⁴	Conversion of CsA to SRL	More frequent in the SRL group (2 vs. 1); difference not significant	Metastatic gastric adenocarcinoma SRL: 1 Lung adenocarcinoma SRL: 1 Two patients (2.4%) Angiosarcoma CsA: 1 Kaposi Sarcoma CsA: 1	BK virus infection CsA: 1 SRL: 1	NR	Proteinuria (>1 g per 24 hr) CsA: 2; SRL: 3	No difference in mean blood pressure, lipids level at 6 months	Diabetes showed a significant association with more severe fibrosis: 92% (12/13) of diabetic patients had IF grade >I at 1 year compared to 49% (53/108) in non-diabetic recipients. Gastrointestinal disorders reported in six cases (6.5%) in the SRL group and three (3.5%) in the CsA group

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Durrbach et al. 2008 ⁸⁵	Conversion from CsA to SRL	NR	Prostate cancer SRL: 1 patient Kaposi's sarcoma CsA: 1	CMV infection CsA: 4; SRL: 0 patients; p=0.12	NR	Proteinuria (>1 g per 24 hr) CsA: 2; SRL: 3	No significant differences in blood pressure and total lipid panels	Lymphocele CsA: 2%; SRL: 24.2%; p=0.04) Pancytopenia CsA: 0%; SRL: 12.1%; p=0.005) Abdominal pain CsA: 2.8%; SRL: 15.2%; p=0.1 Aphthous stomatitis CsA: 0%; SRL: 12.1%; p=0.05 Epistaxis CsA: 0%; SRL: 12.1%; p=0.05

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Barsoum et al. 2007 ⁸⁶	Conversion from CsA to SRL	SRL: 3.6% CsA: 8.1% Authors report no significant difference	Lung malignancy SRL: 2.7%; CsA: 0%; authors report no significant difference Prostate malignancy SRL: 2.7%; CsA: 0%; authors report no significant difference	Herpes viral infection SRL: 15.8%; CsA: 21.1%; authors report no significant difference Pneumonia SRL: 11.8%; CsA: 10.8%; authors report no significant difference	Cardiovascular events SRL: 1.3% (Arm A) CsA: 8.1% (Arm B)	Proteinuria SRL: 36.8%; CsA: 18.6%; p<0.05	Hypertension SRL: 52.6%; CsA: 91.8%; p<0.05 Hyperlipidemia (peak cholesterol >7.75 mmol/L); SRL: 32.9%; CsA: 23.7%; p<0.05 Thrombotic microangiopathy SRL: 1.3% CsA: 0% Deep venous thrombosis SRL: 7.9% CsA: 13.5% Pulmonary embolism SRL: 2.6% CsA: 5.4% Oral ulcers SRL: 13.2% CsA: 5.4% Rectal ulcers SRL: 1.3% CsA: 0% >2-fold elevation of ALT SRL: 11.8% CsA: 10.8% >2-fold elevation of AST SRL: 6.6% CsA: 2.7% >2-fold elevation of GGT SRL: 21.1% CsA: 21.6%	

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Dudley et al. 2005 ⁹⁰	Conversion from CsA to MMF	NR	NR	CMV MMF: 1 CsA: 1 Herpes zoster MMF+ CsA: 11 Herpes simplex MMF+ CsA: 3 Candida albicans MMF+ CsA: 5 Chronic Hepatitis B MMF: 1 (lead to death) UTI MMF: 10 (14%) CsA: 5 (7%)	Myocardial Infarction MMF: 1 (lead to death)	NR	Significant differences in cholesterol in MMF group vs. CsA group. Lower blood pressure observed in MMF group vs. CsA group. Hypotension MMF: 11 (15%) CsA: 4 (6%) Hypertension MMF: 5 (7%) CsA: 8 (11%)	Diarrhea MMF: 33 (45%) CsA: 4 (6%) Abdominal Pain MMF: 17 (23%) CsA: 8 (11%) Anemia MMF: 16 (22%) CsA: 6 (9%) Weight Loss MMF: 11 (15%) Vomiting/Nausea MMF: 12 (16%) CsA: 6 (9%) Anorexia MMF: 7 (10%) CsA: 4 (6%) Polycystic Kidney disease MMF: 1 (lead to death)

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Watson et al. 2005 ⁷⁴	Conversion from CNI to SRL	NR	NR	Chest infection CNI: 2/19 SRL: 4/19 Herpes stomatitis CNI: 1/19 SRL: 2/19 UTI CNI: 4/19 SRL: 6/19	NR	Lower levels of proteinuria after conversion to SRL	No significant changes in blood pressure and total cholesterol levels.	Acneiform rash SRL: 2 Diarrhea CNI: 4/19 SRL: 6/19 Acute gout CNI: 2/19 SRL: 1/19 Pulmonary embolism SRL: 1/19 Bone pain CNI: 2/19 SRL: 3/19 Coryza CNI: 1/19 SRL: 7/19 Dysmenorrhoea SRL: 3/19 Epistaxis CNI: 1/19 SRL: 3/19 Indigestion CNI: 3/19 SRL: 2/19 Mouth ulcers SRL: 6/19 Gum hypertrophy CNI: 5/19 Vomiting CNI: 2/19 SRL: 2/19

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Bakker et al. 2003 ⁸⁷ Followup to Hollander 1995	Conversion from CsA to AZA	NR	Skin cancer CsA 15.2% vs AZA 16%; p=0.5	NR	Cardiovascular mortality 15 year followup CsA: 21.2%; AZA: 23.3%, no significant difference 42.2% in the CsA group and 36.2% in the AZA group had at least one vascular event (p=0.57)	Proteinuria (<1g/day), after 15 years CsA: 14 AZA: 15 Proteinuria (>1g/day), after 15yrs CsA: 1 AZA: 2	Hypertension AZA: 1 No significant differences in total cholesterol and blood pressure.	Gout (n=1) and hypertension (n=1) led authors to convert one patients medication to AZA and "accept lower cyclosporine trough levels in another" During follow-up, 15 patients in the cyclosporine group had their medications changed; in 13 of them (87%), the reason for this change was cyclosporine nephrotoxicity.
MacPhee et al. 1998 ⁸⁸	Conversion from CsA to AZA	NR	Total malignancies AZA: 2 (2%) CsA: 2 (1.8%)	CMV AZA: 1 Serious infections requiring hospitalization were lower in AZA group. CsA: 42 AZA: 31 Total infections AZA: 5 (4.9%) CsA: 3 (2.6%)	Cardiovascular events CsA: 19 AZA: 21; no significant difference	NR	No significant differences in total cholesterol and blood pressure.	NR

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Hilbrands et al. 1996 ⁸⁹	Conversion from CsA to AZA	NR	NR	NR	NR	NR	Antihypertensive therapy CsA: 19 (56%) AZA: 29 (64%) p<0.01	<u>6 months post-transplant</u> Excessive hair growth CsA: 59; AZA-Pred: 24; p<0.01 Swollen face CsA: 12; AZA-Pred: 33 Stiff or painful muscles CsA: 74; AZA-Pred: 36; p<0.01 Tingling in hands CsA: 15; AZA-Pred: 16 Headache CsA: 18; AZA-Pred: 31 Swollen ankles CsA: 26; AZA-Pred: 16 Shortness of breath CsA: 18; AZA-Pred: 31 Difficulty sleeping CsA: 24; AZA-Pred: 22 Bruises CsA: 15; AZA-Pred: 29 Heartburn CsA: 6; AZA-Pred: 20 Dizziness CsA: 0; AZA-Pred: 20; p<0.05 <u>12 months post-transplant</u> Excessive hair growth CsA: 32; AZA-Pred: 7; p<0.01 Swollen face CsA: 9; AZA-Pred: 20

Table E-8. Adverse events reported in conversion studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
								Stiff or painful muscles CsA: 35; AZA-Pred: 31 Tingling in hands CsA: 2; AZA-Pred: 9 Headache CsA: 18; AZA-Pred: 18 Swollen ankles CsA: 15; AZA-Pred: 13 Shortness of breath CsA: 15; AZA-Pred: 16 Difficulty sleeping CsA: 21; AZA-Pred: 16 Bruises CsA: 9; AZA-Pred: 33; p<0.05 Heartburn CsA: 9; AZA-Pred: 22 Dizziness CsA: 6; AZA-Pred: 13

AZA=azathioprine; CsA=cyclosporine; Pred=prednisone

Table E-9. Study design characteristics of withdrawal studies

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Chadban et al. 2014 ²³	Withdrawal of CsA	CsA and EC-MPS withdrawn + EVR (8-12 ng/mL) + STER	CsA (C2 target 500-700 ng/mL) + EC-MPS (1,440 mg) + STER	NR	Basiliximab	2 months	Excluded age>65, PRA>50%, retransplants
Asberg et al. 2012 ⁹⁹	Withdrawal of CsA	CsA withdrawn "in steps over a four-wk period" + MMF (\geq 2,000 mg) + STER (prednisolone)	CsA (75-125 ng/mL) + MMF withdrawn + STER (prednisolone)	NR	NR	>1 year	Excluded PRA >20%
Mourer et al. 2012 ⁹⁷	Withdrawal of CNI	CsA (C2 target 600-800 ng/mL) or TAC (100-140 μ g·hr/mL) withdrawn by 50% reduction followed after 2 weeks by elimination + MMF (MPA-AUC ₀₋₁₂ target 60-90 μ g·hr/mL) + STER (prednisolone 5-10 mg)	CsA (C2 target 600-800 ng/mL) or TAC (100-140 μ g·hr/mL) + MMF withdrawn by 50% reduction followed after 2 weeks by elimination + STER (prednisolone 5-10 mg)	NR	NR	Minimum 6 months	Excluded PRA >60%
Flechner et al. 2011 ¹⁰⁴	Withdrawal of TAC	TAC (6-15 ng/mL) withdrawn by 25% reduction weekly until elimination + SRL (8-15 ng/mL before, 12-20 ng/mL after TAC withdrawal) + STER (5mg)	TAC (5-15 ng/mL) + MMF (1,000-2,000 mg) + STER (5 mg)	IA	Daclizumab	13 weeks	NR
Freitas et al. 2011 ¹⁰⁵	Withdrawal of TAC	TAC (5-8 ng/mL) withdrawn over 4 weeks + SRL (12-20 ng/mL) + STER (prednisone 10 mg)	TAC (5-8 ng/mL) + SRL (12-20 ng/mL) + STER (prednisone 10 mg) withdrawn over 4 weeks	NR	None	3 months	Excluded PRA >50%
Pascual et al. 2008 ⁹³	Withdrawal of CNI	TAC (5-10 ng/mL) or CsA (100-200 ng/mL) withdrawn by 25-50% reduction on day of randomization, followed by elimination 7-14 days after + MMF (1,000-2,000 mg) or EC-MPS (720-1,440 mg) + STER (methylprednisolone 5-7.5 mg)	TAC (5-10 ng/mL) or CsA (100-200 ng/mL) + MMF (1,000-2,000 mg) or EC-MPS (720-1,440 mg) + STER (methylprednisolone 5-7.5 mg)	NR	Alemtuzumab	Between 2 and 16 months	Excluded PRA >10%

Table E-9. Study design characteristics of withdrawal studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Ekberg et al. 2007a ²⁴	Withdrawal of CsA	CsA withdrawn by 33% reduction each month + MMF (2,000 mg) + STER (prednisone 5 mg)	CsA (100–200 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	NR	Daclizumab in intervention group	4 months	Excluded PRA >20%, retransplants
Hazzan et al. 2006 ⁹⁴ (1 year follow up to Hazzan et al. 2005 ¹⁰⁶)	Withdrawal of CsA	CsA (100–300 ng/mL) withdrawn by 25% reduction weekly until elimination + MMF (2,000 mg) + STER (prednisone 0.10–0.15 mg/kg)	CsA (100–300 ng/mL) + MMF (2,000 mg) withdrawn by 25% reduction weekly until elimination + STER (prednisone 0.10–0.15 mg/kg)	NR	ATG	3 months	Excluded PRA >30%
Suwelack et al. 2004 ⁹⁸	Withdrawal of CNI	CsA (80–120 ng/mL) or TAC (4–7 ng/mL) withdrawn by 33% reduction every 2 weeks until elimination + MMF (2,000 mg) + STER (prednisone ≥5 mg)	CsA (80–120 ng/mL) or TAC (4–7 ng/mL) + MMF (2,000 mg) + STER (prednisone ≥5 mg)	NR	NR	Minimum 1 year	All patients had chronic allograft dysfunction
Stallone et al. 2003 ⁹⁵	Withdrawal of CsA	CsA (150–250 ng/mL) withdrawn + SRL (10–15 ng/mL) + STER (prednisone 5 mg)	CsA (150–250 ng/mL) + SRL (10–15 ng/mL) + STER (prednisone 5 mg)	NR	NR	3 months	NR
Abramowicz et al. 2002 ¹⁰⁰	Withdrawal of CsA	CsA (100–200 ng/mL) withdrawn by 33% reduction every 6 weeks until elimination + MMF (2,000 mg) + STER (mean dose 13 mg)	CsA (100–200 ng/mL) + MMF (2,000 mg) + STER (mean dose 7.5 mg)	NR	NR	Between 12 and 30 months	Excluded PRA >50%
Gonwa et al. 2002 ¹⁰²	Withdrawal of CsA	CsA (100–150- ng/mL) withdrawn by 25% reduction weekly until elimination + SRL (10–20 ng/mL) + STER (0.15 mg/kg)	CsA (150–250 ng/mL) + SRL (fixed dose 2 mg) + STER (0.15 mg/kg)	IA HPLC, Mass Spectrometry	NR	2 months	NR
Schnuelle et al. 2002 ⁹⁶	Withdrawal of CsA	CsA (150–250 ng/mL) withdrawn by 33% reduction every 3 weeks until elimination + MMF (2,000 mg) + STER (7.5–10 mg)	CsA (100–250 ng/mL) + MMF withdrawn by 500 mg reduction every two weeks until elimination + STER (7.5–10 mg)	IA	None used	3 months	Excluded PRA >50%
Smak Gregoor et al. 2002 ¹⁰¹ Roodnat et al. 2014 ¹²⁶	Withdrawal of CsA	CsA (125–175 ng/mL) withdrawn by 50% reduction followed after 2 weeks by elimination + MMF (2,000 mg) + STER (prednisone)	CsA (125–175 ng/mL) + MMF (2,000 mg) + STER (prednisone) maintained or withdrawn over 10 weeks	IA	None used	Minimum 6 months	NR

Table E-9. Study design characteristics of withdrawal studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Johnson et al. 2001 ¹⁰³	Withdrawal of CsA	CsA (150–300 ng/mL) withdrawn “over the course of 4–6 weeks” + SRL (20–30 ng/mL) + STER (5–10 mg)	CsA (75–200 ng/mL) + SRL (>5 ng/mL) + STER (5–10 mg)	IA	NR	3 months	NR

AUC₀₋₁₂=area under the curve 0-12 hours; CNI=calcineurin inhibitors; CsA=cyclosporine; EC-MPS=enteric-coated mycophenolate sodium; EVR=everolimus; mg/kg=milligram per kilogram; MMF=mycophenolate mofetil group; MPA=medroxyprogesterone acetate; MPS=mycophenolate sodium; ng/mL=nanogram per milliliter; NR=not reported; PRA=panel reactive antibody; SRL=sirolimus; STER=steroid; TAC=tacrolimus; µg·hr/mL=micrograms per hour per milliliter

Table E-10. Study population characteristics of withdrawal studies

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Chadban et al. 2014 ²³	Withdrawal of CsA	Asia Australia New Zealand	49	47	Deceased: 52 Living related: 51 Living unrelated: 21	48 vs. 46	71%	51%	NR
Asberg et al. 2012 ⁹⁹	Withdrawal of CsA	Norway	20	19	Deceased: 21 Living: 18	63 vs. 54	67%	NR	NR
Mourer et al. 2012 ⁹⁷	Withdrawal of CNI	Netherlands	79	79	Deceased: 95 Living: 63	52 vs. 53	70%	NR	34% vs. 34%
Flechner et al. 2011 ¹⁰⁴	Withdrawal of TAC	Worldwide	152	139	Deceased: 181 Living related: 67 Living unrelated: 43	48 vs. 48	65%	74%	13% vs. 15%
Freitas et al. 2011 ¹⁰⁵	Withdrawal of TAC	Brazil	23	24	Living related and unrelated	35 vs. 35	57%	55%	NR
Pascual et al. 2008 ⁹³	Withdrawal of CNI	USA	20	20	Deceased: 23 Living related: 11 Living unrelated: 6	55 vs. 54	80%	100%	20% vs. 20%
Ekberg et al. 2007a ⁹⁴	Withdrawal of CsA	Worldwide	179	173	Deceased: 273 Living related: 56 Living unrelated: 23	47 vs. 49	62%	82%	17% vs. 22%
Hazzan et al. 2006 ⁹⁴ Hazzan et al. 2005 ¹⁰⁶)	Withdrawal of CsA	France	54	54	Deceased	45 vs. 42	63%	NR	NR

Table E-10. Study population characteristics of withdrawal studies (continued)

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Suwelack et al. 2004 ⁹⁸	Withdrawal of CNI	Germany	18	20	NR	48 vs. 49	74%	100%	NR
Stallone et al. 2003 ⁹⁵	Withdrawal of CsA	Italy	20	20	Deceased	40 vs. 47	NR	100%	40% vs. 45%
Abramowicz et al. 2002 ¹⁰⁰	Withdrawal of CsA	Worldwide	85	85	Deceased: 154 Living: 16	45 vs. 48	59%	96%	NR
Gonwa et al. 2002 ¹⁰²	Withdrawal of CsA	USA Europe	100	97	Deceased	45 vs. 45	57%	77%	NR
Schnuelle et al. 2002 ⁹⁶	Withdrawal of CsA	Germany	44	40	NR	45 vs. 51, p=0.02	64%	NR	18% vs. 20%
Smak Gregoor et al. 2002 ¹⁰¹ Roodnat et al. 2014 ¹²⁶	Withdrawal of CsA	Netherlands	63	149	Deceased: 160 Living: 52	52 vs. 51	66%	NR	NR
Johnson et al. 2001 ¹⁰³	Withdrawal of CsA	Australia Canada Europe	215	215	Deceased: 370 Living related: 37 Living unrelated: 14	45 vs. 46	64%	94%	19% vs. 22%

CNI=calcineurin inhibitors; CsA=cyclosporine; NR=not reported; TAC=tacrolimus

Table E-11. Clinical outcomes of withdrawal studies

Reference	Length of Follow-up	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Chadban et al. 2014 ²³	1 year	15/49 vs. 6/47, p<0.05 Banff (year not reported): Grade 1A: 7 vs. 3 Grade 1B: 5 vs. 4 Grade 2A: 6 vs. 0 Grade 2B: 1 vs. 1 Grade 3: 0 vs. 1 Unspecified: 0 vs. 2	0 vs. 2	0 vs. 1	65.1±15.4 vs. 67.1±18.2, p<0.05 (Nankivell)	NR	24 vs. 8
Asberg et al. 2012 ⁹⁹	7 years	6/20 vs. 0/19, p=0.02	5 vs. 1, p=NS	6 vs. 6	NR	1 year: 120±59 vs. 104±23, p=NS 7 years: 87±24 vs. 116±24, p=0.01	7 vs. 4
Mourer et al. 2012 ⁹⁷	3 years	6 months: 3/79 vs. 1/79 1 year: 4 vs. 1 3 years: 4 vs. 2	1 vs. 1	4 vs. 6	1 year: 61.1±1.8 vs. 52.9±1.8, p<0.01 3 years: 59.5±2.1 vs. 51.1±2.1, p<0.01 (MDRD)	NR	11 vs. 7, p=NS

Table E-11. Clinical outcomes of withdrawal studies (continued)

Reference	Length of Follow-up	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Flechner et al. 2011 ¹⁰⁴	2 years	1 year: 23/152 vs. 11/139 2 years: 26 vs. 17	17 vs. 7, p=NS	8 vs. 5	1 year: 59.1±23.9 vs. 62.0±22.1, p=NS 2 years: 58.3 vs. 62.2, p=NS (Nankivell)	No difference	52 vs. 31
Freitas et al. 2011 ¹⁰⁵	1 year	2/21 vs. 1/24 Banff 97: Grade 1A: 1 vs. 0 Grade 2A: 1 vs. 1	0	1 vs 1	63.4±10.5 vs. 60.0±11.5, p=NS (Nankivell)	114.92±30.94 vs. 129.95±22.98, p=NS	5 vs. 3
Pascual et al. 2008 ⁹³	1 year	2/20 vs. 0/20 Banff 97: Grade 1A: 1 Grade 2A: 1	0	0	72.1±11.6 vs. 68.0±12.1, p=NS Change from baseline: 3.9±9.7 vs. 4.3±11.5, p=NS	1.52±0.64 vs. 1.45±0.30, p=NS	NR
Ekberg et al. 2007a ²⁴	1 year	68/179 vs. 48/173, p<0.05	12 vs. 9	8 vs. 5	50.9±6.4 vs. 48.6±6.9	1.7 mg/dL vs. 1.6 mg/dL	NR
Hazzan et al. 2006 ⁹⁴ Hazzan et al. 2005 ¹⁰⁶	2 years	1 year: 10/54 vs. 3/54, p<0.05 2 years: 12/54 vs. 3/54 Banff 97: Grade 1: 9 vs. 2 Grade 2: 1 vs. 1 NR: 2	1 year: 0 2 year: 4 vs. 1, p=NS	0	1 year: 49.1±17.8 vs. 40.1±11.1, p<0.05 2 years: 45.6±21.6 vs. 37.7±11.0, p<0.05 (aMDRD)	NR	12 vs. 18, p=NS
Suwelack et al. 2004 ⁹⁸	9 months	0	0 vs. 3	NR	NR	As measured by the slope of the reciprocal of serum creatinine, renal function significantly improved in the intervention group and deteriorated in the control group: 0.00585±0.01122 vs. -0.00728±0.01105, p<0.01	NR
Stallone et al. 2003 ⁹⁵	1 year	2/20 vs. 2/20	0	0	3 months: 57.1±16.3 vs. 57.8±18.9 (Nankivell) 1 year: 66±17 vs. 54±14, p<0.01	3 months: 1.6±0.4 vs. 1.9±0.4 1 year: 1.3±0.3 vs. 2.0±0.3, p<0.01	NR

Table E-11. Clinical outcomes of withdrawal studies (continued)

Reference	Length of Follow-up	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Abramowicz et al. 2002 ¹⁰⁰	9 months	9/85 vs. 2/85, p<0.05 Grade 1: 5 vs. 1 Grade 2: 1 vs. 1 Grade 3: 1 vs. 0 Fine needle aspirate: 2 vs. 0	0	1 vs. 0	Intervention group 2.3 mL/min higher than control, p=NS (Nankivell) Intervention group 4.5 mL/min higher than control, p=NS (Cockcroft-Gault)	Change from baseline: -1 vs. 4, p=NS	NR
Gonwa et al. 2002 ¹⁰²	1 year	6 months: 18/100 vs. 15/97, p=NS 1 year: 22 vs. 18, p=NS	5 vs. 7	4 vs. 3	6 months: 64.2 vs. 55.9, p<0.01 1 year: 65.3 vs. 56.4, p<0.01 (Nankivell)	6 months: 1.59±0.07 vs. 1.93±0.12, p<0.01 1 year: 1.64±0.12 vs. 1.99±0.15, p=NS	NR
Schnuelle et al. 2002 ⁹⁶	1 year	5/44 vs. 2/40 Banff 93: Grade 1: 2 vs. 2 Grade 2: 3 vs. 0	1 vs. 0	0	6 months: 76.4±16.9 vs. 66.1±12.2, p<0.01 1 year: 73.2±14.9 vs. 61.9±11.8, p<0.01 (Nankivell)	6 months: 115.4±33.3 vs. 127.8±30.8, p=NS 1 year: 120.7±32.5 vs. 138.3±30.8, p<0.05	NR
Smak Gregoor et al. 2002 ¹⁰¹ Roodnat et al. 2014 ¹²⁶	15 years	18 months: 14/63 vs. 4/149, p<0.01 Banff 93: Grade 1: 5 vs. 3 Grade ≥2: 9 vs. 1	18 months: 2 vs. 3 15 years: 17 vs. 26, p=NS	18 months: 0 vs. 4 15 years: 31 vs. 61, p=NS	Median, 6 months: 66 vs. 63 vs. 58 (CsA withdrawal + MMF + STER vs. CsA + MMF + withdrawal of STER) 18 months: 64 vs. 65 vs. 58 (Cockcroft-Gault)	Median, 6 months: 117 vs. 124 vs. 137 18 months: 123 vs. 125 vs. 137	18 months: 18 vs. 12, p<0.05 15 years: 20 vs. 69
Johnson et al. 2001 ¹⁰³	1 year	21/215 vs. 9/215, p<0.05	6 vs. 9	4 vs. 6	62.7±1.5 vs. 56.6±1.3, p<0.01	141.6±5.3 vs. 158.1±4.2, p<0.01	58 vs. 39, p<0.05

aMDRD=abbreviated modification of diet in renal disease; MDRD=modification of diet in renal disease; NR=not reported; NS=not significant

Table E-12. Adverse events reported in withdrawal studies

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Chadban et al. 2014 ²³	Withdrawal of CsA	18 vs. 13	2 vs. 1	CMV: 2 vs. 4 All infections: 33 vs. 34	NR	1 vs. 1	No difference between groups for cholesterol	No difference between groups for GI, anemia
Asberg et al. 2012 ⁹⁹	Withdrawal of CsA	NR	4/20 vs 1/19	Sepsis: 0 vs. 2	Cardiovascular cause of death: 1 vs. 2	NR	NR	NR
Mourer et al. 2012 ⁹⁷	Withdrawal of CNI	4 vs. 5	4 vs. 6	34 vs. 25, p=NS	NR	NR	No difference in BP, cholesterol	Anemia: 18 vs. 9, p=0.06

Table E-12. Adverse events reported in withdrawal studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Flechner et al. 2011 ¹⁰⁴	Withdrawal of TAC	27/120 vs. 12/110, p<0.05	7/152 vs. 5/139	All infections: 61.2% vs. 66.9%	NR	17 vs. 9	Cholesterol and triglycerides higher in intervention group	Intervention group had higher incidence of edema, hyperlipidemia, tremor, hyperkalemia, lymphoceles, thrombocytopenia, acne Control group had higher incidence of diarrhea; no difference for anemia, hypertension
Freitas et al. 2011 ¹⁰⁵	Withdrawal of TAC	"similar between groups"	0	"similar between groups"	NR	3 vs. 2	No difference in BP, triglycerides, dyslipidemia; total cholesterol higher in intervention group, p=0.02	Intervention group: higher incidence (NS) of lymphocele or lymphorrhea, stomatitis, headache, leucopenia, thrombocytopenia, dyslipidemia Control group: higher incidence (NS) of diarrhea, anemia, cramps; 1 case of nephrotoxicity in control group
Pascual et al. 2008 ⁹³	Withdrawal of CNI	0/20 vs. 2/20	NR	CMV: 3 vs. 2 Herpes zoster: 0 vs. 1 Gastroenteritis: 0 vs. 1 UTI: 2 vs. 0 Sinusitis: 1 vs. 0	NR	Increased in both groups, difference NS	No difference	2 cases of nephrotoxicity in control group
Ekberg et al. 2007a ²⁴	Withdrawal of CsA	NR	4 (including 2 posttransplant lymphoproliferative disorder) vs. 1	CMV: 23 vs. 24 Candida: 8 vs. 16 Herpes simplex: 14 vs. 11 Herpes zoster: 3 vs. 9	NR	NR	No difference	No difference for lymphocele, hypertension
Hazzan et al. 2006 ⁹⁴ Hazzan et al. 2005 ¹⁰⁶	Withdrawal of CsA	NR	NR	NR	NR	No difference	NR	15 cases of nephrotoxicity in control group
Suwelack et al. 2004 ⁹⁸	Withdrawal of CNI	NR	0	CMV: 1 vs. 6 Herpes zoster: 0 vs. 2	2 vs. 0	0.50±0.55 vs. 1.50±0.48, p=0.01	BP lower in intervention group	Lower incidence of GI, anemia in intervention group

Table E-12. Adverse events reported in withdrawal studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Stallone et al. 2003 ⁹⁵	Withdrawal of CsA	5/20 vs. 5/20	NR	NR	NR	NR	No difference	NR
Abramowicz et al. 2002 ¹⁰⁰	Withdrawal of CsA	NR	1/85 vs. 4/85	8 vs. 11 Includes CMV, herpes, zoster, herpes simplex, candida (specific data not reported)	NR	NR	No difference for BP, triglycerides; improved LDL and total cholesterol for intervention group	Higher incidence of diarrhea in intervention group
Gonwa et al. 2002 ¹⁰²	Withdrawal of CsA	No difference	4/100 vs. 0/97 (2 skin carcinomas, 1 lymphoproliferative disease, 1 renal cell carcinoma)	"no significant differences in the rates of clinically important infections"	NR	NR	Systolic BP lower in intervention group ($p<0.05$) but no difference in diastolic BP; total cholesterol higher in intervention group ($p<0.05$); no difference in triglycerides	Intervention group: higher incidence of atrial fibrillation, diarrhea, abnormal liver function, thrombocytopenia, hypokalemia Control group: significantly higher incidence of edema, dyspnea, hypertension, hypervolemia, hypomagnesemia, hirsutism
Schnuelle et al. 2002 ⁹⁶	Withdrawal of CsA	4/44 vs. 6/40	NR	CMV: 3 vs. 1 Herpes simplex: 1 vs. 1 Herpes zoster: 1 vs. 0 Oral candidiasis: 1 vs. 0 PCP: 0 vs. 1 UTI: 4 vs. 13 Upper respiratory tract: 2 vs. 1 Pneumonia: 3 vs. 3 Septicemia: 0 vs. 3 Other: 1 vs. 1	NR	NR	Lower BP and improved lipids in intervention group	No difference in GI, hirsutism; 1 case of nephrotoxicity in control group

Table E-12. Adverse events reported in withdrawal studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Smak Gregoor et al. 2002 ¹⁰¹ Roodnat et al. 2014 ¹²⁶	Withdrawal of CsA	NR	2 skin carcinomas, 1 lymphoma	18 months: CMV: 4 vs. 3 Herpes simplex: 5 vs. 13 Herpes zoster: 2 vs. 3 Candida stomatitis: 3 vs. 4 Oesofagitis: 0 vs. 2 Pneumonia: 3 vs. 8 Bronchitis: 2 vs. 18 UTI: 36 vs. 64 Upper respiratory tract: 13 vs. 32 Gastrointestinal: 4 vs. 6 Skin: 7 vs. 9 Other: 1 vs. 5 Sepsis: 3 vs. 2	NR	No difference between groups, or vs. baseline	Triglycerides lower in intervention group at 18 months, p<0.05	Nephrotoxicity: 1 vs. 7
Johnson et al. 2001 ¹⁰³	Withdrawal of CsA	9 vs. 7	2 (lymphoma and "other") vs. 7 (4 skin cancer, 1 lymphoma, 2 "other")	CMV: 8 vs. 7 Sepsis: 4 vs. 8 Pneumonia: 15 vs. 9 Herpes simplex: 13 vs. 10 Herpes zoster: 1 vs. 11 Oral moniliasis: 5 vs. 7	NR	NR	No difference in BP, cholesterol, triglycerides	Hypertension lower in intervention group; thrombocytopenia and hypokalemia higher in intervention group Nephrotoxicity: 5 vs. 15, p<0.05

BP=blood pressure; CMV=cytomegalovirus=CNI=calcineurin inhibitors; CsA=cyclosporine; GI=gastrointestinal; NR=not reported; NS=not significant; PCP=pneumocystis carinii pneumonia; UTI=urinary tract infection; TAC=tacrolimus

Table E-13. Study design characteristics of avoidance studies

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Vincenti et al. 2010 ¹⁰⁷ BENEFIT Follow-ups: Larsen et al. 2010 ¹²⁷ Vincenti et al. 2012 ¹²⁸ Rostaing et al. 2013 ¹²⁹	Avoidance of CsA	Belatacept (5 mg/kg) in more intensive or less intensive schedule of administration + MMF (2,000 mg) + STER (≥ 2.5 mg)	CsA (100–250 ng/mL) + MMF (2,000 mg) + STER (≥ 2.5 mg)	NR	Basiliximab	Immediate	Excluded PRA >50%, or PRA >30% for retransplants
Durrbach et al. 2010 ¹⁰⁸ BENEFIT-EXT Follow-ups: Larsen et al. 2010 ¹²⁷ Pestana et al. 2012 ¹³⁰ Charpentier et al. 2013 ¹³¹	Avoidance of CsA	Belatacept (5 mg/kg) in more intensive or less intensive schedule of administration + MMF (2,000 mg) + STER (≥ 2.5 mg)	CsA (100–250 ng/mL) + MMF (2,000 mg) + STER (≥ 2.5 mg)	NR	Basiliximab	Immediate	Extended criteria donors: Age ≥ 60 years; or age ≥ 50 years with at least 2 risk factors (cerebro-vascular accident, hypertension or serum creatinine >1.5 mg/dL); or anticipated cold ischemia time ≥ 24 hours; or donation after cardiac death
Refaie et al. 2011 ¹¹³	Avoidance of TAC	SRL (10–15 ng/mL)	TAC (4–8 ng/mL)	NR	Alemtuzumab	Immediate	Excluded retransplants
Glotz et al. 2010 ¹¹⁰	Avoidance of TAC	rATG induction (1.25–1.5 mg/kg) + SRL (12–20 ng/mL) + MMF (1,500 mg) + STER (prednisolone 0.1 mg/kg)	TAC (5–9 ng/mL) + MMF (1,500 mg) + STER (prednisolone 0.1 mg/kg)	HPLC	rATG for intervention group only	Immediate	Excluded age >65 , PRA >50%
Ekberg et al. 2007b ⁴	Avoidance of CsA	SRL (4–8 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	CsA (100–200 ng/mL) + MMF (2,000 mg) + STER (prednisone 5 mg)	IA (CNI) HPLC (SRL)	Daclizumab in intervention group	Immediate	Excluded age >75 , PRA >20%
Schaefer et al. 2006 ¹¹¹	Avoidance of TAC	SRL (8–12 ng/mL) + MMF (2,000 mg) + STER (prednisone 10 mg)	TAC (8–12 ng/mL) + MMF (2,000 mg) + STER (prednisone 5–10 mg) or withdrawal of STER	NR	ATG	Immediate	NR

Table E-13. Study design characteristics of avoidance studies (continued)

Reference	Type of Intervention	Intervention Regimen	Control Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Flechner et al. 2002 ¹⁰⁹	Avoidance of CsA	SRL (5–10 ng/mL) + MMF (2,000 mg) + STER (prednisone 7.5 mg)	CsA (200–250 ng/mL) + MMF (2,000 mg) + STER (prednisone 7.5 mg)	IA (CsA) HPLC-MS (SRL)	Basiliximab	Immediate	Excluded age>70, retransplants
Groth et al. 1999 ¹¹²	Avoidance of CsA	SRL (15 ng/mL) + AZA (2 mg/kg) + STER (prednisone or prednisolone 10 mg)	CsA (100–200 ng/mL) + AZA (2 mg/kg) + STER (prednisone or prednisolone 10 mg)	IA (CsA) HPLC (SRL)	Not used	Immediate	Excluded age>60, PRA >70%

ATG/rATG=antithymocyte globulin/rabbit antithymocyte globulin; AZA=azathioprine; CNI=calcineurin inhibitors; CsA=cyclosporine; HPLC=high performance liquid chromatography; IA=immunoassay; mg/kg=milligram per kilogram; mg/mL=milligram per milliliter; MMF=mycophenolate mofetil group; ng/mL=nanogram per milliliter; NR=not reported; PRA=panel reactive antibody; SRL=sirolimus; TAC=tacrolimus

Table E-14. Study population characteristics of avoidance studies

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Vincenti et al. 2010 ¹⁰⁷ BENEFIT Follow-ups: Larsen 2010 ¹²⁷ Vincenti et al. 2012 ¹²⁸ Rostaing et al. 2013 ¹²⁹	Avoidance of CsA	Worldwide	445	221	Deceased: 280 Living related: 280 Living unrelated: 106	44 vs. 43	70%	61%	15% vs. 18%
Durrbach et al. 2010 ¹⁰⁸ BENEFIT-EXT Follow-ups: Larsen et al. 2010 ¹²⁷ Pestana et al. 2012 ¹³⁰ Charpentier et al. 2013 ¹³¹	Avoidance of CsA	Worldwide	359	184	NR	57 vs. 56	68%	76%	47% vs. 49%
Refaie et al. 2011 ¹¹³	Avoidance of TAC	Egypt	10	11	Living related	30 vs. 34	75%	NR	NR
Glotz et al. 2010 ¹¹⁰	Avoidance of TAC	France Belgium	71	70	Deceased	48 vs. 47	62%	84%	NR
Ekberg et al. 2007b ⁴	Avoidance of CNI	Worldwide	399	390	Deceased: 512 Living related: 231 Living unrelated: 46	45 vs. 46	65%	93%	NR
Schaefer et al. 2006 ¹¹¹	Avoidance of TAC	USA	41	78	Deceased Living	NR	NR	NR	NR
Flechner et al. 2002 ¹⁰⁹	Avoidance of CsA	USA	31	30	Deceased: 40 Living related: 14 Living unrelated: 7	48 vs. 47	66%	67%	13% vs. 17%
Groth et al. 1999 ¹¹²	Avoidance of CsA	Europe	41	42	Deceased	48 vs. 42, p=0.02	65%	93%	17% vs. 7%

BENEFIT=Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial; CNI=calcineurin inhibitors; CsA=cyclosporine; NR=not reported; TAC=tacrolimus

Table E-15. Clinical outcomes of avoidance studies

Reference	Length of Follow-up	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, µmol/L	Regimen Changed
Vincenti et al. 2010 ¹⁰⁷ BENEFIT Follow-ups: Larsen et al. 2010 ¹²⁷ Vincenti et al. 2012 ¹²⁸ Rostaing et al. 2013 ¹²⁹	5 years	1 year: 88/445 vs. 16/221 Banff 97: Grade 1A: 11 vs. 3 Grade 1B: 11 vs. 5 Grade 2A: 33 vs. 6 Grade 2B: 30 vs. 2 Grade 3: 3 vs. 0 2 years: 92 vs. 20 3 years: 92 vs. 21 5 years: 93 vs. 22	1 year: 9 vs. 8 2 years: 12 vs. 8 3 years: 19 vs. 10 5 years: 19 vs. 13	1 year: 10 vs. 7 2 years: 15 vs. 13 3 years: 19 vs. 15 5 years: 24 vs. 22	1 year measured GFR: 65.0±30.0 vs. 63.4±27.7 vs. 50.4±18.7, p<0.01 2 years measured GFR: 65.0±27.2 vs. 67.9±29.9 vs. 50.5±20.5 3 years eGFR (MDRD): 65.2±26.3 vs. 65.8±27.0 vs. 44.4±23.6 5 years eGFR (MDRD): 74.1±18.9 vs. 76.4±19.0 vs. 53.0±17.2, p<0.01	NR	1 year: 133 overall 2 years: 167 overall
Durrbach et al. 2010 ¹⁰⁸ BENEFIT-EXT Follow-ups: Larsen et al. 2010 ¹²⁷ Pestana et al. 2012 ¹³⁰ Charpentier et al. 2013 ¹³¹	5 years	1 year: 64/359 vs. 26/184 Banff 97: Grade 1A: 4 vs. 2 Grade 1B: 9 vs. 2 Grade 2A: 27 vs. 17 Grade 2B: 24 vs. 5 2 years: 64 vs. 28 3 years: 66 vs. 29 5 years: 69 vs. 29	1 year: 33 vs. 20 2 years: 38 vs. 22 3 years: 39 vs. 23 5 years: 42 vs. 28	1 year: 12 vs. 8 2 years: 24 vs. 12 3 years: 37 vs. 17 5 years: 51 vs. 23	1 year measured GFR: 52.1±21.9 vs. 49.5±25.4 vs. 45.2±21.1, p<0.01 for more intensive vs. CsA 2 years measured GFR: 51.5±22.2 vs. 49.7±23.7 vs. 45.0±27.2 5 years eGFR: 55.9 vs. 59.0 vs. 44.6	NR	1 year: 149 overall 2 years: 189 overall
Refaie et al. 2011 ¹¹³	4 years	2/10 vs. 5/11 Antibody-mediated rejection: 2 vs. 2 Borderline: 0 vs. 2 Grade 1A: 0 vs. 1	2 vs. 1	0 vs. 1	1.83±0.88 mL/second vs. 1.38±0.48 mL/second, p<0.05	114.9±17.7 vs. 114.9±26.4, p=NS	2 vs. 8
Glotz et al. 2010 ¹¹⁰	1 year	12/71 vs. 9/70 Banff 97: Grade 1A: 6 vs. 4 Grade 1B: 2 vs. 3 Grade 2A: 3 vs. 1 Grade 2B: 1 vs. 0 Grade 3: 0 vs. 1	10 vs. 3, p<0.05	3 vs. 2	6 months eGFR: 72.7 vs. 65.2, p<0.05 (Nankivell) 1 year eGFR: 68 vs. 62, p=NS 6 months CrCl: 68.8±21.6 vs. 57.5 ±19.4, p<0.05 (Cockcroft-Gault)	NR	33 vs. 7, p<0.001

Table E-15. Clinical outcomes of avoidance studies (continued)

Reference	Length of Follow-up	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, $\mu\text{mol/L}$	Regimen Changed
Ekberg et al. 2007 ^b	1 year	6 months: 141/399 vs. 94/390 12 months: 160 vs. 117	33 vs. 32	12 vs. 13	56.7 \pm 26.9 vs. 57.1 \pm 25.1 (Cockcroft-Gault) 47.5 \pm 26.1 vs. 46.2 \pm 23.1 (MDRD)	NR	NR
Schaefer et al. 2006 ¹¹¹	1 year	5/41 vs. 5/78	3 vs. 1	2 vs. 0	NR	3 months: 1.3 \pm 0.4 vs. 1.5 \pm 0.4 (with STER) vs. 1.4 \pm 0.4 (without STER) p=0.01 for intervention group vs. control group with STER	NR
Flechner et al. 2002 ¹⁰⁹	1 year	2/31 vs. 5/30 Borderline: 1 vs. 2 Grade 1A: 1 vs. 2 Grade 2A: 1	1 vs. 1	1 vs. 0	6 months: 77.8 \pm 21.0 vs. 64.1 \pm 19.1, p<0.01 1 year: 81.1 \pm 23.9 vs. 61.1 \pm 14.6, p<0.01 (Cockcroft-Gault)	6 months: 1.29 \pm 0.30 vs. 1.74 \pm 0.81 mg/dL, p<0.01 1 year: 1.32 \pm 0.33 vs. 1.78 \pm 0.76 mg/dL, p<0.01	0 vs. 3
Groth et al. 1999 ¹¹²	1 year	6 months: 17/41 vs. 16/42 Banff 93: Grade 1: 6 vs. 9 Grade 2: 9 vs. 6 Grade 3: 2 vs. 1	1 vs. 4	0 vs. 1	3 months: 66.1 \pm 3.3 vs. 54.2 \pm 3.3, p<0.05 6 months: 66.7 \pm 3.6 vs. 59.0 \pm 3.4, p=NS 1 year: 69.5 \pm 4.1 vs. 58.7 \pm 3.6, p=NS (Nankivell)	3 months: 126.2 \pm 11.4 vs. 159.2 \pm 11.2, p<0.05 6 months: 126.2 \pm 8.7 vs. 135.4 \pm 8.2, p=NS 1 year: 115.8 \pm 8.9 vs. 133.5 \pm 7.7, p=NS	24 vs. 19

CrCl=creatinine clearance; CsA=cyclosporine; GFR/eGFR=glomerular filtration rate/estimated glomerular filtration rate; MDRD=modification of diet in renal disease; mg/dL=milligrams per deciliter; NS=not significant; STER=steroids

Table E-16. Adverse events reported in avoidance studies

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Vincenti et al. 2010 ¹⁰⁷ BENEFIT Follow-ups: Larsen et al. 2010 ¹²⁷ Vincenti et al. 2012 ¹²⁸ Rostaing et al. 2013 ¹²⁹	Avoidance of CsA	1 year: 18 vs. 16, p=NS 2 years: no change	1 year: 9 vs. 1 2 years: 27 vs. 11 3 years: 28 vs. 12 Post-transplant lymphoproliferative disorder: 5 vs. 1 5 years: 20 vs. 12 (neoplasms included)	1 year: CMV: 30 vs. 19 BK: 13 vs. 9 Pneumonia: 5 vs. 5 Sepsis: 3 vs. 4 UTI: 117 vs. 50 Upper respiratory tract: 46 vs. 26 Nasopharyngitis: 20 vs. 20 Influenza: 32 vs. 10 Oral candidiasis: 18 vs. 13 Bronchitis: 16 vs. 5 Gastroenteritis: 13 vs. 7 2 years: CMV: 24 vs. 7 Pneumonia: 9 vs. 9 UTI: 26 vs. 23 3 years: CMV: 48 vs. 25 BK: 28 vs. 18 Herpes simplex: 6 vs. 2 Herpes zoster: 18 vs. 11 Oral candidiasis: 26 vs. 14 Onchomycosis: 19 vs. 6 Candidiasis: 14 vs. 2 Body tinea: 8 vs. 1 5 years: Pneumonia: 7 vs. 3 UTI: 11 vs. 5 Pyelonephritis: 5 vs. 3	5 years: 8 vs. 4	NR	BP, cholesterol, triglycerides better in intervention group at 1, 2, and 5 years	No difference in GI, lymphocele, pyrexia at 1, 2, and 5 years No difference in metabolic, vascular, nervous system disorders at 5 years

Table E-16. Adverse events reported in avoidance studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/ Lipids	Other
Durrbach et al. 2010 ¹⁰⁸ BENEFIT-EXT Follow-ups: Larsen et al. 2010 ¹²⁷ Pestana et al. 2012 ¹³⁰ Charpentier et al. 2013 ¹³¹	Avoidance of CsA	1 year: 8 vs. 6 8 vs. 11, p<0.05 for less intensive belatacept vs. CsA	1 year: Post-transplant lymphoproliferative disorder: 3 vs. 0 2 years: 27 vs. 17 3 years: 31 vs. 19 Post-transplant lymphoproliferative disorder: 5 vs. 0 5 years: 40 vs. 22 Post-transplant lymphoproliferative disorder: 8 vs. 1	1 year: CMV: 45 vs. 24 Pneumonia: 15 vs. 5 UTI: 112 vs. 62 Upper respiratory tract: 22 vs. 14 Nasopharyngitis: 33 vs. 13 Oral candidiasis: 12 vs. 12 Bronchitis: 27 vs. 11 Gastroenteritis: 11 vs. 10 2 years: CMV: 33 vs. 12 Pneumonia: 14 vs. 6 UTI: 38 vs. 17 Pyelonephritis: 10 vs. 8 3 years: CMV: 59 vs. 31 BK: 19 vs. 9 Herpes simplex: 5 vs. 3 Herpes zoster: 32 vs. 9 Oral candidiasis: 18 vs. 12 Onchomycosis: 9 vs. 3 Candidiasis: 9 vs. 6 Body tinea: 5 vs. 7 5 years: CMV: 8 vs. 3 BK: 5 vs. 1 Herpes (all): 18 vs. 10 Pneumonia: 7 vs. 3 Sepsis: 4 vs. 4 UTI: 10 vs. 5 Pyelonephritis: 5 vs. 6 Central nervous system infections: 3 vs. 0 Fungal infections: 31 vs. 12	NR	NR	1 year: BP, triglycerides, non-HDL cholesterol better in intervention group; no difference for LDL and HDL cholesterol 3 years: BP lower in intervention group; no difference in cholesterol or triglycerides 5 years: BP lower in intervention group; total and non-HDL cholesterol lower in intervention group; no difference in HDL cholesterol; triglycerides lower in intervention group	No difference in GI, anemia, leukopenia, hyperkalemia, pyrexia at 1 and 3 years
Refaie et al. 2011 ¹¹³	Avoidance of TAC	3/10 vs. 2/11	0 vs. 1 (Kaposi sarcoma)	1 (tuberculosis) vs. 1 (hepatitis B)	NR	7/9 vs. 3/6, p=0.2	No difference in cholesterol	NR

Table E-16. Adverse events reported in avoidance studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Glotz et al. 2010 ¹¹⁰	Avoidance of TAC	11 vs. 14	2 vs. 1 (all lymphoproliferative disorder)	CMV: 1 vs. 14, p<0.001 Herpes: 9 vs. 5, p=NS BK: 2 vs. 0 Pneumonia: 5 vs. 1	NR	No difference in mean values; but 36% of intervention vs. 14% of control have proteinuria (p<0.05)	No difference in hypertension or hyperlipidemia Hypercholesterolemia higher in intervention group	Higher incidence of edema, hypokalemia, anemia, thrombocytopenia in intervention group Higher incidence of hyperkalemia, leukopenia in control group No difference in stomatitis
Ekberg et al. 2007b ⁴	Avoidance of CNI	25 vs. 23	10 vs. 5 Post-transplant lymphoproliferative disorder, oral mucosa, renal-cell, non-small-cell lung, small-cell lung, breast, colon, T-cell non-Hodgkin's, B-cell non-Hodgkin's, ovarian vs. 2 basal-cell, squamous-cell, oral mucosa, Kaposi's sarcoma	All "opportunistic infections" (per study designation): 77 vs. 100 CMV: 23 vs. 55 Candida: 19 vs. 29 Herpes simplex: 23 vs. 21 All other infections: 200 vs. 208 UTI: 88 vs. 109 Pneumonia: 19 vs. 18 Nasopharyngitis: 15 vs. 22	11 vs. 15	20 vs. 9	No differences	No difference for anemia, leukopenia, edema, pyrexia, disorders of the nervous system, respiratory system, or vascular system Higher incidence of lymphoceles and serious GI events in low dose SRL group
Schaefer et al. 2006 ¹¹¹	Avoidance of TAC	6/41 vs. 5/78, p<0.05	NR	Viral infections (CMV, BK): 0 vs. 2	NR	NR	Cholesterol, lipids, triglycerides higher in intervention group compared with steroid-free control group	NR

Table E-16. Adverse events reported in avoidance studies (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Flechner et al. 2002 ¹⁰⁹	Avoidance of CsA	NR	NR	CMV: 3 vs. 2	NR	NR	No difference in BP; cholesterol and triglycerides higher in both groups compared with baseline, but no difference between groups	NR
Groth et al. 1999 ¹¹²	Avoidance of CsA	1/41 vs. 1/42	0 vs. 2 (stomach carcinoid, basal cell carcinoma)	CMV: 6 vs. 5 Herpes simplex: 10 vs. 4 Herpes zoster: 0 vs. 1 Oral candida 3 vs. 0 PCP: 0 vs. 1 UTI: 17 vs. 12 Septicemia: 6 vs. 1 Pneumonia: 7 vs. 1	NR	NR	Hypercholesterolemia and hypertriglyceridemia higher in intervention group ($p<0.01$, both); no difference in hypertension	Hypokalemia, thrombocytopenia, leukopenia, arthralgia higher in intervention group; no difference in anemia

BENEFIT=Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial; BP=blood pressure; BK=BK polyomavirus; CMV=cytomegalovirus; CNI=calcineurin inhibitors; CsA=cyclosporine; GI=gastrointestinal; HDL=high density lipoprotein; LDL=low density lipoprotein; NR=not reported; NS=not significant; PCP=pneumocystis carinii pneumonia; SRL=sirolimus; TAC=tacrolimus; UTI=urinary tract infection

Table E-17. Study design characteristics of studies comparing two regimens

Reference	Type of Intervention	Minimization Regimen	Comparator Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Burkhalter et al. 2012 ¹¹⁹	Minimization of TAC Withdrawal of TAC	Minimization: TAC (4–8 ng/mL) + SRL (4–8 ng/mL) + EC-MPS (>2 mg/mL)	Withdrawal: Withdrawal of TAC by 50% reduction and then elimination over 2 weeks + SRL (8–12 ng/mL) + EC-MPS (>2 mg/mL)	NR	Basiliximab	3 months	NR
Han et al. 2011 ¹¹⁴	Minimization of CsA Conversion from CsA to SRL	Minimization: CsA (150–200 ng/mL if 6 months–1 year post-transplant; 100–150 ng/mL if 1–2 years post-transplant, and 50–100 ng/mL if >2 years post-transplant) + MMF + STER	Conversion: Conversion from CsA to SRL (5–8 ng/mL) + MMF + STER	NR	NR	Minimum 6 months	All patients had chronic allograft dysfunction; Excluded retransplants

Table E-17. Study design characteristics of studies comparing two regimens (continued)

Reference	Type of Intervention	Minimization Regimen	Comparator Regimen	Analytical Method for Measuring Therapeutic Drug Levels	Induction Therapy	Time from Transplant to Start of Intervention	Special Inclusion/Exclusion Criteria
Pankewycz et al. 2011 ¹¹⁶	Minimization of TAC Conversion from TAC to SRL	Minimization: TAC (4–6 ng/mL) + MMF (1,440 mg) + STER (prednisone 5 mg)	Conversion: Conversion from TAC to SRL (5–10 ng/mL) + MMF (1,440 mg) + STER (prednisone 5 mg)	NR	rATG	3 months	Excluded PRA >30%, retransplants
Cataneo-Davila et al. 2009 ¹¹⁷	Minimization of CNI Conversion from CNI to EVR	Minimization: CNI (CsA or TAC) at 80% reduction from baseline + EVR (3–8 ng/dL) + STER (prednisone 5–10 mg)	Conversion: Conversion from CNI to EVR (5–10 ng/dL) + STER (prednisone 5–10 mg) + either MMF or AZA	NR	NR	Minimum 6 months	All patients had chronic allograft dysfunction
Liu et al. 2007 ¹¹⁵	Minimization of CsA Conversion from CsA to SRL	Minimization: CsA (dose 1.5–2 mg/kg) + MMF (1,500 mg) + STER (prednisone 5 mg)	Conversion: Conversion from CsA to SRL (5–10 ng/mL) + MMF (1,500 mg) + STER (prednisone 5 mg)	FPLA (CsA) HPLC (SRL)	NR	Minimum 1 year	All patients had chronic allograft dysfunction; excluded age >60, PRA >10%
Hamdy et al. 2005 ¹²⁰	Minimization of TAC Avoidance	Minimization: TAC (3–7 ng/mL) + SRL (6–12 ng/mL) + STER (prednisolone 0.1 mg/kg)	Avoidance: SRL (10–15 ng/mL) + MMF (2,000 mg) + STER (prednisolone 0.1 mg/kg)	NR	Basiliximab	Within 24 hours	Excluded retransplants
Stallone et al. 2005 ¹¹⁸	Minimization of CNI Conversion from CNI to SRL	Minimization: CsA (C2 target 400–500 ng/mL) or TAC (4–6 ng/mL) + MMF (1,000 mg) + STER (prednisone 5 mg)	Conversion: Conversion from CNI to SRL (6–10 ng/mL) + STER (prednisone 5 mg)	IA (CNI) HPLC (SRL)	NR	1–3 years	All patients had chronic allograft dysfunction
Lo et al. 2004 ¹²¹	Minimization of TAC Avoidance	Avoidance: SRL (12–15 ng/mL) + MMF (2,000 mg) + STER (5 mg)	Minimization: TAC (3–6 ng/mL) + SRL (10–15 ng/mL) + STER (5 mg)	HPLC-MS	rATG	Within 2 days	High risk population: 71% African-American; 30% age >50 years; 47% with delayed graft function; all donors deceased

CNI=calcineurin inhibitors; CsA=cyclosporine; EC-MPS=enteric-coated mycophenolate sodium; EVR=everolimus; FPIA=fluorescence polarization immunoassay; HPLC=high performance liquid chromatography; IA=immunoassay; mg/kg=milligram per kilogram; mg/mL=milligram per milliliter; MS=mass spectrometry; MMF=mycophenolate mofetil group; MPS=mycophenolate sodium; ng/mL=nanogram per milliliter; NR=not reported; PRA=panel reactive antibody; rATG=rabbit antithymocyte globulin; SRL=sirolimus; STER=steroid; TAC=tacrolimus

Table E-18. Study population characteristics in studies comparing regimens

Reference	Type of Intervention	Country/Region	N, Intervention	N, Control	Donor Type	Mean Age, Intervention vs. Control	Gender: % Male	Race: % Caucasian	Delayed Graft Function %, Intervention vs. Control
Burkhalter et al. 2012 ¹¹⁹	Minimization of TAC Withdrawal of TAC	Switzerland	Minimization: 19 Withdrawal: 18	NR	Deceased: 9 Living: 28	Minimization: 55 Withdrawal: 43 p<0.05	86%	NR	NR
Han et al. 2011 ¹¹⁴	Minimization of CsA Conversion from CsA to SRL	China	Minimization: 29 Conversion: 22	NR	Deceased	Minimization: 44 Conversion: 45	75%	100% Asian	NR
Pankewycz et al. 2011 ¹¹⁶	Minimization of TAC Conversion from TAC to SRL	USA	Minimization: 29 Conversion: 23	NR	Deceased: 24 Living: 28	Minimization: 57 Conversion: 51	69%	13% African-American	Minimization: 17% Conversion: 4%
Cataneo-Davila et al. 2009 ¹¹⁷	Minimization of CNI Conversion from CNI to EVR	Mexico	Minimization: 10 Conversion: 10	NR	Deceased: 5 Living: 15	Minimization: 29 Conversion: 39	45%	NR	NR
Liu et al. 2007 ¹¹⁵	Minimization of CsA Conversion from CsA to SRL	China	Minimization: 64 Conversion: 56	NR	Deceased	Minimization: 36 Conversion: 35	75%	100% Asian	NR
Hamdy et al. 2005 ¹²⁰	Minimization of TAC Avoidance	Egypt	Minimization: 65 Avoidance: 67	NR	Living	Minimization: 32 Avoidance: 32	75%	NR	NR
Stallone et al. 2005 ¹¹⁸	Minimization of CNI Conversion from CNI to SRL	Italy	Minimization: 50 Conversion: 34	NR	NR	Minimization: 43 Conversion: 49	NR	NR	Minimization: 24% Conversion: 29%
Lo et al. 2004 ¹²¹	Minimization of TAC Avoidance	USA	Minimization: 41 Avoidance: 29	NR	Deceased	Minimization: 44 Avoidance: 42	57%	71% African-American	Minimization: 56% Avoidance: 34%

CNI=calcineurin inhibitors; CsA=cyclosporine; EVR=everolimus; NR=not reported; SRL=sirolimus; TAC=tacrolimus

Table E-19. Clinical outcomes of studies comparing regimens

Reference	Type of Intervention	Length of Follow-up	Biopsy Proven Acute Rejection	Graft Loss	Patient Death	Mean eGFR or Creatinine Clearance, mL/min (Method)	Mean Serum Creatinine, $\mu\text{mol/L}$	Regimen Changed
Burkhalter et al. 2012 ¹¹⁹	Minimization of TAC Withdrawal of TAC	6 months	Minimization: 1 Withdrawal: 2	NR	NR	Minimization: 52 Withdrawal: 45 (Median)	NR	Minimization: NR Withdrawal: 4
Han et al. 2011 ¹¹⁴	Minimization of CsA Conversion from CsA to SRL	4 years	Minimization: 2 Conversion: 2	"graft survival estimate": Minimization: 55% Conversion: 77%	NR	eGFR declined in minimization group over baseline, $p<0.05$; eGFR higher in conversion group compared with minimization group, $p<0.05$	NR	NR
Pankewycz et al. 2011 ¹¹⁶	Minimization of TAC Conversion from TAC to SRL	1 year	Minimization: 0 Conversion: 1	Minimization: 0 Conversion: 1	NR	Minimization: 74 ± 15 Conversion: 66 ± 18	NR	Minimization: 1 Conversion: 4
Cataneo-Davila et al. 2009 ¹¹⁷	Minimization of CNI Conversion from CNI to EVR	1 year	Minimization: 1 Conversion: 0	Minimization: 0 Conversion: 0	Minimization: 0 Conversion: 0	Minimization: 76.2 ± 22.6 Conversion: 66.2 ± 13.7	Minimization: 1.24 ± 0.4 Conversion: 1.25 ± 0.3	Minimization: 1 Conversion: 0
Liu et al. 2007 ¹¹⁵	Minimization of CsA Conversion from CsA to SRL	2 years	NR	"graft survival ratio was markedly higher in conversion group"	NR	Minimization: 37 ± 9.7 Conversion: 50 ± 12.3 $p<0.05$	Minimization: 210.2 ± 66.9 Conversion: 150.4 ± 54.8 $p<0.05$	NR
Hamdy et al. 2005 ¹²⁰	Minimization of TAC Avoidance	2 years	Minimization: 12 Avoidance: 9	Minimization: 4 Avoidance: 3	Minimization: 2 Avoidance: 0	Minimization: 79.6 ± 25.5 Avoidance: 94.9 ± 28.9 $p<0.05$	Minimization: 1.43 ± 0.40 Avoidance: 1.25 ± 0.39 $p<0.05$	Minimization: 20 Avoidance: 6
Stallone et al. 2005 ¹¹⁸	Minimization of CsA Conversion from CsA to SRL	2 years	Minimization: 0 Conversion: 0	Minimization: 8 Conversion: 1	Minimization: 0 Conversion: 0	Minimization: 47.8 ± 17.6 Conversion: 53.1 ± 21.5	Minimization: 1.99 ± 0.59 Conversion: 1.86 ± 0.60	NR
Lo et al. 2004 ¹²¹	Minimization of TAC Avoidance	1 year	Minimization: 4 Avoidance: 2	Minimization: 8 Avoidance: 3	Minimization: 1 Avoidance: 0	Minimization: 52.9 ± 22.8 Avoidance: 72.4 ± 20.0 $p<0.05$	NR	Minimization: 5 Avoidance: 8

CNI=calcineurin inhibitors; CsA=cyclosporine; EVR=everolimus; eGFR=estimated glomerular filtration rate; mL/min=milliliter per minute; NR=not reported; SRL=sirolimus; TAC=tacrolimus; $\mu\text{mol/L}$ =micromoles per liter

Table E-20. Adverse events reported in studies comparing regimens

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Burkhalter et al. 2012 ¹¹⁹	Minimization of TAC Withdrawal of TAC	NR	NR	NR	NR	NR	Triglycerides higher in withdrawal group; no difference for cholesterol	NR
Han et al. 2011 ¹¹⁴	Minimization of CsA Conversion from CsA to SRL	NR	NR	1 pneumonia in conversion group	NR	NR	Cholesterol and triglycerides increased in conversion group	NR
Pankewycz et al. 2011 ¹¹⁶	Minimization of TAC Conversion from TAC to SRL	NR	NR	Minimization: 1 BK Conversion: 1 pneumonia, 1 pyelonephritis	NR	1 severe case in conversion group	1 patient in conversion group changed regimen due to elevated triglycerides	NR
Cataneo-Davila et al. 2009 ¹¹⁷	Minimization of CNI Conversion from CNI to EVR	NR	NR	"no severe infections"	NR	NR	Cholesterol and triglycerides higher than baseline in conversion group; no difference in minimization group	NR
Liu et al. 2007 ¹¹⁵	Minimization of CsA Conversion from CsA to SRL	NR	NR	NR	NR	Higher than baseline in both groups, but no difference between groups	Cholesterol and triglycerides higher in conversion group than minimization group; no difference for BP	NR
Hamdy et al. 2005 ¹²⁰	Minimization of TAC Avoidance	Minimization: 18 Avoidance: 13	NR	Minimization: 14 UTI, 3 tuberculosis, 4 fungal Avoidance: 5 herpes zoster, 23 UTI, 1 tuberculosis, 2 ungal	NR	Minimization: 9 Avoidance: 20	Cholesterol and hyperlipidemia higher in avoidance group	Higher incidence of GI in minimization group; no difference for leukopenia
Stallone et al. 2005 ¹¹⁸	Minimization of CNI Conversion from CNI to SRL	No difference	NR	"no major infections occurred"	NR	Minimization: 0.92±0.52 Conversion: 1.2±0.69	No differences	NR

Table E-20. Adverse events reported in studies comparing regimens (continued)

Reference	Type of Intervention	New Onset Diabetes	Malignancy	Infection	Major Adverse Cardiac Events	Proteinuria	Blood Pressure/Lipids	Other
Lo et al. 2004 ¹²¹	Minimization of TAC Avoidance	Minimization: 10 Avoidance: 5	Minimization: 1 post-transplant lymphoproliferative disorder Avoidance: 1 prostate cancer	No CMV in either group Minimization: 1 sepsis, 4 pneumonia, 2 UTI Avoidance: 4 pneumonia, 2 UTI	NR	NR	Cholesterol, triglycerides, hyperlipidemia increased in both groups over baseline, but no significant differences between groups	No difference for GI, anemia, thrombocytopenia. 28 patients in minimization group and 17 patients in avoidance group were readmitted to hospital

BP=blood pressure; BK=polyomavirus; CMV=cytomegalovirus; CNI=calcineurin inhibitors; CsA=cyclosporine; EVR=everolimus; GI=gastrointestinal; NR=not reported; SRL=sirolimus; TAC=tacrolimus; UTI=urinary tract infection

Table E-21. Risk of bias assessment for studies addressing Key Question 3

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Cai et al. 2014 ⁴⁴	Yes	NR	Yes	NR	NR	NR	Yes	NR	Yes	No	High
Muhlbacher et al. 2014 ⁵⁹	Yes	NR	Yes	NR	NR	NR	Yes	Yes	Yes	No	High
Oh et al. 2014 ⁶²	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	No	Low
Bechstein et al. 2013 ⁶⁷	NR	NR	Yes	NR	NR	Yes	Yes	Yes	Yes	No	High
Chadban et al. 2013 ⁴⁵	NR	NR	Yes	NR	NR	NR	Yes	Yes	Yes	No	High
Cibrik et al. 2013 ⁶⁰	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	Yes	No	Moderate
Takahashi et al. 2013 ⁶¹	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	No	Moderate
Chan et al. 2012 ⁵⁶	Yes	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	No	Moderate
Kamar et al. 2012 ⁵⁷	Yes	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	No	Moderate
Langer et al. 2012 ⁶⁸	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	No	Moderate
Paoletti et al. 2012 ⁶³	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Low
Bertoni et al. 2011 ⁶⁴	NR	NR	Yes	NR	NR	NR	Yes	NR	Yes	Yes	High
Xu et al. 2011 ³⁹	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	NR	High
Etienne et al. 2010 ⁴⁶	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Low

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Fangmann et al. 2010 ⁴⁷	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	NR	Moderate
Gaston et al. 2009 ⁴⁰	Yes	NR	Yes	NR	No	NR	Yes	Yes	Yes	No	High
Salvadori et al. 2009 ⁶⁵	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	No	Moderate
Spagnoletti et al. 2009 ⁴¹	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	High
Bolin et al. 2008 ⁵⁸	Yes	NR	Yes	NR	NR	NR	Yes	Yes	Yes	No	High
Chan et al. 2008 ⁶⁹	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	Yes	No	Moderate
Budde et al. 2007 ⁴⁸	Yes	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	No	Moderate
Cibrik et al. 2007 ⁴⁹	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	No	Moderate
Ghafari et al. 2007 ⁵⁰	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	NR	NR	High
Hernandez et al. 2007 ⁴²	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	Moderate
Frimat et al. 2006 ⁵¹	Yes	NR	Yes	Yes	No	NR	Yes	Yes	Yes	No	Moderate
Frimat et al. 2010 ⁵²											
Tang et al. 2006 ⁴³	Yes	NR	Yes	Yes	NR	Yes	Yes	Yes	NR	No	High
Vathsala et al. 2005 ³⁸	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	No	Moderate

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Lo et al. 2004 ⁷⁰	NR	NR	Yes	NR	NR	NR	Yes	Yes	Yes	NR	High
Nashan et al. 2004 ⁶⁶	NR	NR	Yes	NR	NR	NR	Yes	Yes	No	No	High
Stoves et al. 2004 ⁵³	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	No	Moderate
Pascual et al. 2003 ⁵⁴	NR	NR	Yes	NR	NR	NR	Yes	Yes	Yes	No	High
de Sevaux et al. 2001 ⁵⁵	Yes	Yes	Yes	NR	NR	NR	Yes	Yes	NR	No	High
Bensal et al. 2013 ⁷²	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Low
Chhabra et al. 2013 ⁷⁷	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	High
Silva et al. 2013 ⁷⁸	Yes	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Moderate
Budde et al. 2012 ⁷³	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Low
Budde et al. 2011 ⁹²											
Mjornstedt et al. 2012 ⁸⁰	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	No	Moderate
Nafar et al. 2012 ⁸¹	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	NR	High
Heilman et al. 2011 ⁷⁹	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	No	Moderate
Rostaing et al. 2011 ⁹¹	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	No	High

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Weir et al. 2011 ⁷⁵	Yes	NR	Yes	NR	Yes	NR	Yes	Yes	No	No	High
Guba et al. 2010 ⁸²	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	No	No	Moderate
Bemelman et al. 2009 ⁸³	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	No	Moderate
Schena et al. 2009 ⁷⁶	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	No	No	Moderate
Lebranchu et al. 2011 ¹²⁵ Lebranchu 2009 ⁸⁴	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Low
Durrbach et al. 2008 ⁸⁵	Yes	NR	Yes	Yes	Yes	NR	Yes	Yes	No	No	High
Barsoum et al. 2007 ⁸⁶	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	High
Dudley et al. 2005 ⁹⁰	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	No	No	Moderate
Watson et al. 2005 ⁷⁴	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Low
Bakker et al. 2003 ⁸⁷	NR	NR	Yes	Yes	No	NR	Yes	Yes	Yes	NR	High
MacPhee et al. 1998 ⁸⁸	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	NR	High
Hilbrands et al. 1996 ⁸⁹	NR	NR	Yes	Yes	Yes	Yes	No	Yes	No	No	High
Quality of Life											

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Hilbrands et al. 1996 ⁸⁹ Renal function, BPAR	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	No	No	High
Asberg et al. 2012 ⁹⁸	NR	NR	NR	NR	Yes	NR	Yes	NR	Yes	No	High
Mourer et al. 2012 ⁹⁷	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	No	Moderate
Flechner et al. 2011 ¹⁰⁴	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	High
Freitas et al. 2011 ¹⁰⁵	Yes	NR	Yes	NR	NR	NR	Yes	Yes	Yes	No	High
Pascual et al. 2008 ⁹³	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Low
Hazzan et al. 2006 ^{94,106})	NR	NR	Yes	Yes	NR	NR	Yes	Yes	Yes	Yes	High
Suwelack et al. 2004 ⁹⁸	NR	NR	Yes	NR	NR	NR	Yes	Yes	No	No	High
Stallone et al. 2003 ⁹⁵	NR	NR	Yes	Yes	NR	NR	Yes	Yes	Yes	NR	High
Abramowicz et al. 2002 ¹⁰⁰	Yes	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	Moderate
Gonwa et al. 2002 ¹⁰²	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	No	High
Schnuelle et al. 2002 ⁹⁶	NR	NR	Yes	NR	NR	NR	Yes	Yes	Yes	NR	High

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Smak Gregoor et al. 2002 ¹⁰¹ Roodnat et al. 2014 ¹²⁶	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes	No	Moderate
Johnson et al. 2001 ¹⁰³	NR	NR	Yes	Yes	NR	NR	Yes	Yes	Yes	No	High
Vincenti et al. 2010 ^{107,127-129}	Yes	Yes	Yes	NR	No	Yes	Yes	Yes	Yes	No	Moderate
Durrbach et al. 2010 ^{108,127,130,131}	Yes	Yes	Yes	NR	No	Yes	Yes	Yes	Yes	No	Moderate
Refaie et al. 2011 ¹¹³	NR	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	NR	High
Glotz et al. 2010 ¹¹⁰	NR	NR	Yes	Yes	No	NR	Yes	Yes	Yes	No	High
Schaefer et al. 2006 ¹¹¹	NR	NR	Yes	NR	NR	NR	Yes	Yes	NR	NR	High
Flechner et al. 2002 ¹⁰⁹	Yes	NR	Yes	NR	Yes	NR	Yes	Yes	Yes	No	Moderate
Groth et al. 1999 ¹¹²	Yes	Yes	Yes	NR	No	NR	Yes	Yes	Yes	No	Moderate
Chadban et al. 2014 ²³	Yes	Yes	Yes	NR	No	No	Yes	Yes	No	No	High
Holdaas et al. 2011 ²²	Yes	NR	Yes	NR	No	NR	Yes	Yes	Yes	No	High
Ekberg et al. 2007a ³⁴	Yes	Yes	Yes	Yes	No	NR	Yes	Yes	Yes	No	Moderate
Ekberg et al. 2007b ⁴	Yes	Yes	Yes	Yes	No	NR	Yes	Yes	No	No	Moderate

Table E-21. Risk of bias assessment for studies addressing Key Question 3 (continued)

Author, Year	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Did the study enroll all suitable patients or consecutive suitable patients?	Was compliance with treatment ≥85% in both of the study's groups?	Were outcome assessors blinded to the group to which patients were assigned?	Was the outcome measure of interest objective and was it objectively measured?	Was a standard instrument used to measure the outcome?	Was there a ≤15% difference in completion rates in the study's groups?	Was the funding derived from a source that would not benefit financially from results?	Overall Risk of Bias
Burkhalter et al. 2012 ¹¹⁹	Yes	Yes	Yes	NR	No	NR	Yes	Yes	Yes	NR	Moderate
Han et al. 2011 ¹¹⁴	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	High
Pankewycz et al. 2011 ¹¹⁶	NR	NR	Yes	NR	No	NR	Yes	Yes	No	No	High
Cataneo-Davila et al. 2009 ¹¹⁷	NR	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	High
Liu et al. 2007 ¹¹⁵	NR	NR	Yes	NR	NR	NR	Yes	Yes	NR	NR	High
Hamdy et al. 2005 ¹²⁰	NR	NR	Yes	NR	No	NR	Yes	Yes	Yes	NR	High
Stallone et al. 2005 ¹¹⁸	NR	NR	Yes	Yes	NR	Yes	Yes	Yes	NR	Yes	High
Lo et al. 2004 ¹²¹	NR	NR	Yes	NR	No	NR	Yes	Yes	No	No	High

NR= Not reported